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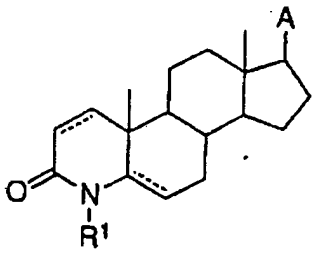
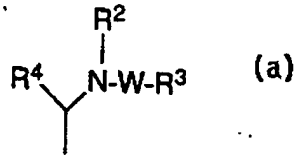
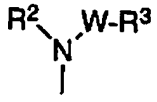
(54) Title: 17-AMINO SUBSTITUTED 4-AZASTEROID 5α-REDUCTASE INHIBITORS



(I)



(a)



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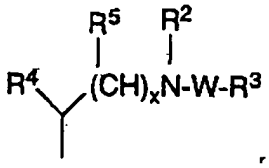

(c)

(57) Abstract

Novel amino substituted 4-azasteroid 5α-reductase inhibitors of formula (I), wherein A is (a), (b) or (c), are claimed as well as pharmaceutically acceptable salts and formulations thereof. These compounds are effective in inhibiting testosterone 5α-reductase(s) and are thus useful in the treatment of a number of hyperandrogenic conditions including benign prostatic hypertrophy, acne, seborrhea, female hirsutism, and male and female pattern baldness (alopecia).

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TITLE OF THE INVENTION

17-AMINO SUBSTITUTED 4-AZASTEROID 5α-REDUCTASE INHIBITORS

BACKGROUND OF THE INVENTION

The present invention is directed to novel amino substituted 4-azasteroidal 5α-reductase inhibitors.

The art reveals that certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, male pattern baldness and benign prostatic hypertrophy, are the result of hyperandrogenic stimulation caused by an excessive accumulation of testosterone or similar androgenic hormones in the metabolic system. Early attempts to provide a chemotherapeutic agent to counter the undesirable results of hyperandrogenicity resulted in the discovery of several steroidal antiandrogens having undesirable hormonal activities of their own. The estrogens, for example, not only counteract the effect of the androgens but have a feminizing effect as well. Non-steroidal antiandrogens have also been developed, for example, 4'-nitro-3'-trifluoromethyl-isobutyranilide. See Neri, et al., Endo., Vol. 91, No. 2 (1972). However, these products, though devoid of hormonal effects. are peripherally active, competing with the natural androgens for receptor sites, and hence have a tendency to feminize a male host or the male fetus of a female host.

It is now known in the art that the principal mediator of androgenic activity in some target organs is 5α-dihydrotestosterone, and that it is formed locally in the target organ by the action of testosterone-5α-reductase. It is also known that inhibitors of testosterone-5α-reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation. A number of 4-azasteroid compounds are known in the art as 5α-reductase inhibitors. For example, See U.S. Patent Nos. 2,227,876, 3,239,417, 3,264,301 and 3,285,918; French Patent No. 1,465,544; Doorenbos and Solomons, J. Pharm. Sci. 62, 4, pp. 638-640 (1973); Doorenbos and Brown, J. Pharm. Sci., 60, 8, pp. 1234-1235

(1971); and Doorenbos and Kim, J. Pharm. Sci. 63, 4, pp. 620-622 (1974).

In addition, U.S. Patent Nos. 4,377,584, 4,220,775, 4,859,681, 4,760,071 and the articles J. Med. Chem. 27, p. 1690-1701 (1984) and J. Med. Chem. 29, 2998-2315 (1986) of Rasmusson, et al., U.S. Patent 4,845,104 to Carlin, et al., and U.S. Patent 4,732,897 to Cainelli, et al. describe 4-aza-17ß- substituted-5α-androstan-3-ones which are said to be useful in the treatment of DHT-related hyperandrogenic conditions.

However, despite the suggestion in the prior art that hyperandrogenic diseases are the result of a single 5α-reductase, there are reports regarding the presence of other 5α-reductase isozymes in both rats and humans. For example, in human prostate, Bruchovsky, et al. (See J. Clin. Endocrinol. Metab. 67, 806-816, 1988) and Hudson (see J. Steroid Biochem. 26, p 349-353, 1987) found different 5α-reductase activities in the stromal and epithelial fractions. Additionally, Moore and Wilson described two distinct human reductases with peaks of activities at either pH 5.5 or pH 7-9. (See J. Biol. Chem. 251, 19, p. 5895-5900, 1976.)

Recently, Andersson and Russell isolated a cDNA which encodes a rat liver 5α-reductase (see J. Biol. Chem. 264 pp. 16249-55 (1989). They found a single mRNA which encodes both the liver and prostatic reductases of rats. The sequence of this rat gene was later used to select a human prostatic cDNA encoding a 5α-reductase termed "5α-reductase 1". (See Proc. Nat'l. Acad. Sci. 87, p. 3640-3644, 1990.)

More recently, a second, more abundant reductase (5α-reductase 2) has been cloned from human prostate with properties identified with the form found in crude human prostatic extracts. (See Nature, 354, p. 159-161, 1991.)

Further, "Syndromes of Androgen Resistance" - The Biology of Reproduction, Vol. 46, p. 168-173 (1992) by Jean O. Wilson indicates that the 5α-reductase I enzyme may be associated with hair follicles.

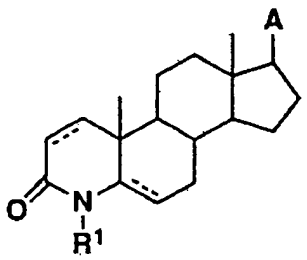
Thus, the art supports the existence of at least two genes for 5α-reductase and two distinct isozymes of 5α-reductase in humans. Both forms are present in prostatic tissue in which, 5α-reductase 2, is the more abundant, whereas the other isozyme, 5α-reductase 1, is believed to be more abundant in scalp tissue.

In the treatment of hyperandrogenic disease conditions, e.g. benign prostatic hyperplasia (BPH) it would be desirable to have one drug entity which is active against both enzymes 1 and 2 in the prostate to substantially inhibit dihydrotesterone (DHT) production. Alternatively, it would be desirable to have a drug entity which is highly selective for inhibiting the scalp associated enzyme 5α-reductase 1, for use in treating diseases of the skin and scalp, e.g., acne and alopecia. This latter drug could thus be used in combination with PROSCAR® (finasteride) which is highly selective for the prostatic enzyme 5α-reductase 2 for combination therapy in the treatment of BPH.

SUMMARY OF THE INVENTION

The present invention is concerned with novel 4-azasteroidal compounds and pharmaceutical compositions and formulations thereof that are useful for inhibiting the 5α-reductase isozymes 1 and 2 and are particularly effective in selectively inhibiting the 5α-reductase 1 associated with the scalp and dually inhibiting both isozymes 1 and 2 in the treatment of benign prostatic hyperplasia, acne, female hirsutism, male pattern baldness, androgenic alopecia, prostatitis, and the prevention and treatment of prostatic carcinoma.

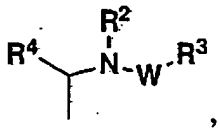
The present invention is concerned with compounds of the formula:

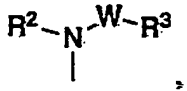


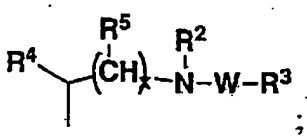
I

and the pharmaceutically acceptable salts thereof, wherein:

A is:

(a)  ,

(b)  , except when R^2 equals H, there is a 5αH and W equals C(O). R^3 can not be C_{1-12} alkyl.

(c)  ; wherein

R^1 is:

H,
methyl or ethyl;

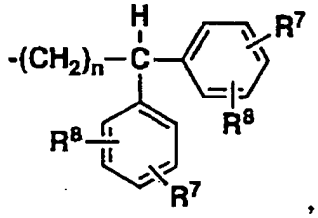
R^2 is:

H, or
C_{1-20} alkyl;

R^3 is:

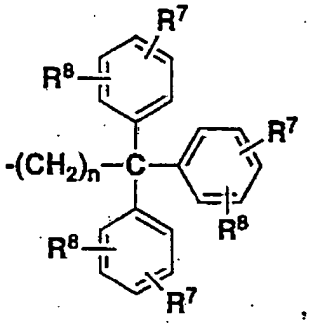
H,
aminoC_1-C4alkyl,
mono C_1-C4alkylaminoC_1-C4alkyl,
di C_1-C4alkylaminoC_1-C4alkyl,

mono C_1-C_4 alkylaminoaryl,
di C_1-C_4 alkylaminoaryl,
C_{1-20} alkyl,
C_{6-14} aryl,
heteroaryl,
C_{6-14} arylC_{1-20}alkyl,
heteroarylC_{1-20}alkyl,
C_{1-20}alkylthioC_{1-20}alkyl,
C_{1-20}alkylsulfinylC_{1-20}alkyl,
C_{1-20}alkyloxycarbonylC_{1-20}alkyl,
carboxylC_{1-20}alkyl,
C_{1-20}alkylcarbonylC_{1-20}alkyl,
carboxylC_{1-20}alkyl,
C_{1-20}alkylcarbonylC_{1-20}alkyl,
C_{3-20}cycloalkyl,
C_{3-20}cycloalkylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
haloC_{1-20}alkyl,
hydroxylC_{1-20}alkyl,
halohydroxylC_{1-20}alkyl,
thiosulfatoC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxyC_{1-20}alkyl,
C_{1-20}alkyloxyC_{1-20}alkyl,
C_{6-14} arylcarbonylC_{6-14}arylC_{1-20}alkyl,
diarylC_{1-20}alkyl of the formula:



, n equals 1-19;

triarylC_{1-20}alkyl of the formula:



, n equals 1-19;

C_{2-20} alkenyl,
C_{2-20} alkenylC_{1-20}alkyl,
heteroarylC_{2-20}alkenyl,
C_{6-14} arylC_{2-20}alkenyl,
C_{2-20}alkynylC_{1-20}alkyl,
C_{6-14} arylC_{2-20}alkynylC_{1-20}alkyl, or
heteroarylC_{2-20}alkynylC_{1-20}alkyl;

R^4 is:

H,
C_{1-20} alkyl,
C_6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy. carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide, halogen or other specific groups as shown herein or

heteroaryl;

R^5 can be the same or different when x is greater than 1 and is:

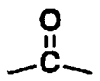
H, or

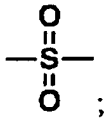
C_{1-12} alkyl;

R^7 or R^8 are:

H,
CH_3,
C_2H_5,
carboxamido,
C_{1-6} alkylthio,
C_1-C_6 alkylsulfinyl,
C_1-C_6 alkylsulfonyl,
OCH_3,
NH_2,
CH_3NH,
$(CH_3)_2N$,
OH,
NO_2,
CN,
F,
acetamido,
Cl,
OC_2H_5,
CF_3,
isopropyl, or
isobutyl; n equals 1-10 and the C_{1-20} alkyl portion is optionally substituted with R^5;

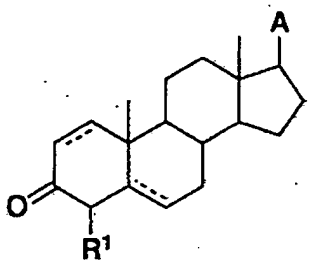
W is:


, or


;

x is an integer from 1-25;
and the dashes indicate a double bond is optionally present.

Advantageously, compounds of the following formula are disclosed:



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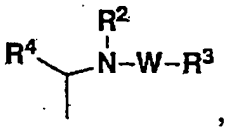
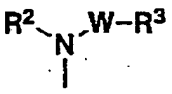
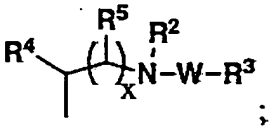
and the pharmaceutically acceptable salts thereof, wherein:

A is:

(a)  ,

(b)  except when R^2 equals H, there is a 5alphaH and W equals C(O), R^3 can not be C_{1-12} alkyl,

(c)  ; wherein

R^1 is:

H,
methyl, or ethyl;

R^2 is:

H, or
C_{1-20}alkyl;

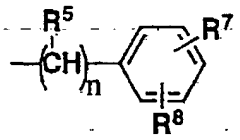
R^3 is:

H,
C_{1-20}alkyl is a straight or branched chain alkane of up to 20 carbon atoms;

C_{6-14} aryl wherein aryl is a mono or polycyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen;

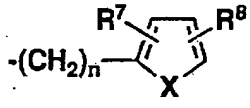
heteroaryl which is a mono or polycyclic system composed of 5- or 6-membered aromatic rings consisting of 1,2, 3 or 4 heteroatoms chosen from N, O, or S and either unsubstituted or substituted with R or independently with hydroxyl, C_{1-20}alkyloxy, C_{1-20}alkyl, benzoyl, carboamide, acetamide, halogens, C_{2-20}alkenyl, cyano, nitro, or haloalkyl directly bonded to the aromatic carbon atoms(s);

C_{6-14} arylC_{1-20}alkyl of the formula:

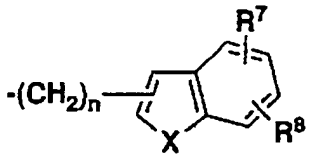


wherein the aromatic ring is optionally and independently substituted with R^7 and R^8 wherein R^7 and R^8 are
H,
CH_3,
C_2H_5,
carboxamido,
C_1-C_6 alkylthio,
C_1-C_6 alkylsulfinyl,
C_1-C_6 alkylsulfonyl,
OCH_3,
NH_2,
CH_3NH,
$(CH_3)_2N$,
OH,
NO_2,
CN,
F,
acetamido,
Cl,
OC_2H_5,
CF_3,
isopropyl, or
isobutyl; n equals 1-10 and the C_{1-20}alkyl portion is optionally substituted with R^5;

HeteroarylC$_{1-20}$alkyl of the formula:



. or



wherein X equals O, S, or NR; and n equals 1-10;

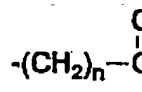
C_{1-20}alkylsulfonylC_{1-20}alkyl,
C_{1-20}alkylthioC_{1-20}alkyl,
C_{1-20}alkylsulfinylC_{1-20}alkyl of the formula:

$-(CH_2)_nS(O)_p-R^9$ wherein R^9 is
CH_3,
C_2H_5,
C_3H_7,
C_4H_9,
isopropyl,
isobutyl,
sec-butyl,
t-butyl,
isopentyl,
neopentyl, or
ixohexyl; n equals 1-15 and p=0-2;

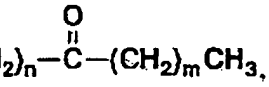
C_{1-20}alkyloxycarbonylC_{1-20}alkyl of the formula:

$-(CH_2)_n-\overset{O}{\overset{\|}{C}}-OR^{10}$ wherein R^{10} is:
CH_3,
C_2H_5,
C_3H_7,
C_4H_9, or
C_5H_{11}; and n equals 1-20;

CarboxylC_{1-20}alkyl of the formula:

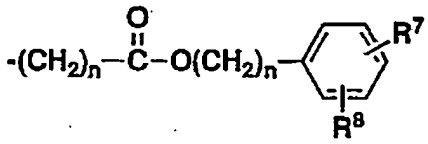

; n = 1-20;

C_{1-20}alkylcarbonylC_{1-20}alkyl of the formula


, n equals 1-20;
m equals 0-19;

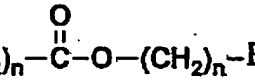
C_{3-20}cycloalkylC_{1-20}alkyl of the formula:
$-(CH_2)_n$-(cycloalkyl) wherein the cycloalkyl protion is a monocyclic, bicyclic, or polycyclic hydrocarbon of up to 20 carbon atoms wherein the rings are optionally substituted with R^1; and n = 1-20;

ArylC_{1-20}alkyloxycarbonylC_{1-20}alkyl of the formula:-



wherein n = 1-20;

HeteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl of the formula:

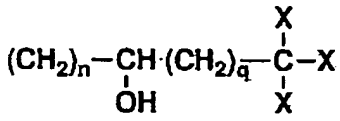

wherein Heteroaryl is as defined and n = 1-20;

haloC_{1-20}alkyl of the formula:
$-(CH_2)_n-CH_2X$ wherein
X equals Br, Cl, F or I; n is 1-19;

hydroxylC_{1-20}alkyl of the formula:

$-(CH_2)_nCH_2OH$; n is 1-19;

halohydroxylC_{1-20}alkyl of the formula:



wherein

n = 1-18

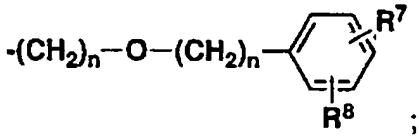
q = 0-18

n + q = 0-18 and

X equals Br, Cl, F or I;

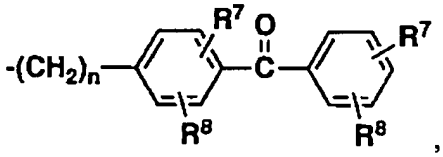
ThiosulfatoC_{1-20}alkyl of the formula:
$-(CH_2)_nCH_2SSO_3Na$; n is 1-19;

ArylC_{1-20}alkyloxyC_{1-20}alkyl of the formula:



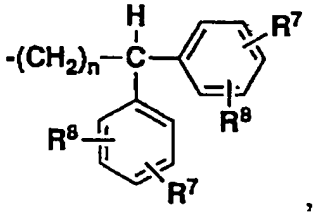
; n is 1-20;

ArylcarbonylarylC_{1-20}alkyl of the formula:



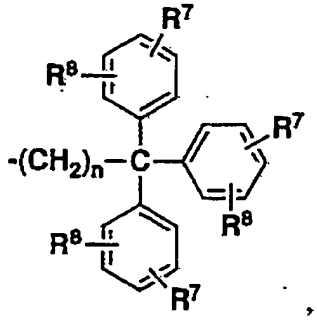
, n equals 1-20;

DiarylC_{1-20}alkyl of the formula:



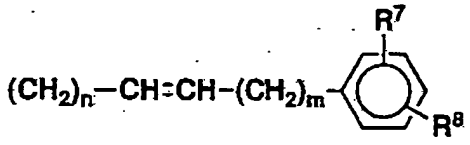
, n equals 0-19;

TriarylC1-20alkyl of the formula:



, n equals 1-19;

Aryl C2-20alkenyl of the formula:



n = 0-18
m = 0-18
m+n = 0-18

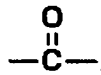
R^4 is

H,
C1-20alkyl,
C6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C1-6 alkyl, arylC1-20alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C1-8alkyloxy, carboxy C0-10alkyl, or halogen or aryl directly substituted independently with amino, mono C1-C4 alkylamino, di C1-C4 alkylamino, mono C1-C4 alkylaminoaryl, di C1-C4 alkylaminoaryl, hydroxyl, haloC1-20alkyl, carboxamido, benzoyl, C1-20alkyloxy, C1-20alkyl, C2-20alkenyl, cyano, nitro, acetamide or halogen; or

heteroaryl;

R^5 can be the same or different when x is greater than one and is;
H, or
C_{1-12}alkyl;

W is:

 , or

 ,

x is an integer from 1-10;

and the dashes indicate a double bond is optionally present.

The present invention is particularly concerned with providing a method of treating the hyperandrogenic conditions of androgenic alopecia, acne vulgaris, seborrhea, and female hirsutism by topical and/or oral administration, and a method of treating all of the above conditions as well as benign prostatic hyperplasia, prostatitis, the prevention and/or treatment of prostatic carcinoma, by oral or parenteral administration, of the novel compounds of the present invention.

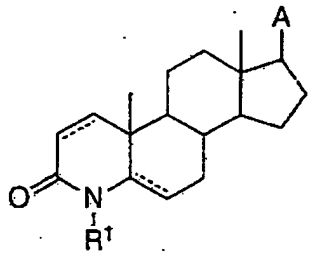
The present invention is thus also concerned with providing suitable topical, oral and parenteral pharmacedutical formulations for use in the novel methods of treatment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention is concerned with novel 4-azasteroidal amide compounds and pharmaceu- tical compositions and formulations thereof that are useful as testosterone 5α-reductase

inhibitors to treat various hyperandrongenic conditions including acne vulgaris, seborrhea, female hirsutism, male pattern baldness, benign prostatic hypertrophy, prostatitis, androgenic alopecia, and the prevention and treatment of prostatic carcinoma. Advantageously, the compounds of the invention may be used to treat scalp disorders by selectively inhibiting 5α-reductase 1 or the compounds may be used as dual inhibitors of 5α reductase 1 and 2 to treat the above disorders.

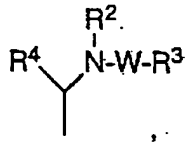
The present invention is concerned with compounds of the formula:

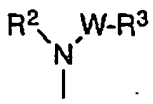


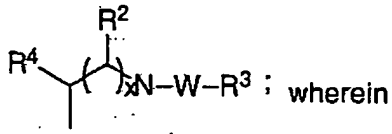
I

and the pharmaceutically acceptable salts thereof, wherein:

A is

a) 

b)  except when R^2 equals H, there is a 5αH and W equals C(O). R^3 can not be C_{1-12} alkyl.

c)  ; wherein

wherein

R^1 is H, methyl or ethyl;

R^2 is H, or C_{1-20} alkyl;

R^3 is:
H,
C_{1-20} alkyl,
C_{5-14} aryl,
heteroaryl,
C_{5-14} arylC_{1-20}alkyl,
heteroarylC_{1-20}alkyl,
C_{1-20}alkyloxyC_{1-20}alkyl,
C_{1-20}alkylthioC_{1-20}alkyl,
C_{1-20}alkyloxycarbonylC_{1-20}alkyl,
C_{1-20} alkylC_{6-14}arylC_{1-20}alkyl,
carboxyC_{1-20}alkyl,
C_{1-20} alkylcarbonylC_{1-20}alkyl,
C_{3-20}cycloalkyl,
C_{3-20} cycloalkylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
haloC_{1-20}alkyl,
hydroxyC_{1-20}alkyl,
halohydroxyC_{1-20}alkyl,
thiosulfatoC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxyC_{2-20}alkynylC_{1-20}alkyl,
C_{6-14} arylC_{2-20}alkynylC_{1-20}alkyl,
heteroarylC_{2-20}alkynylC_{1-20}alkyl,
diarylC_{1-20}alkyl,
triarylC_{1-20}alkyl,
C_{2-20}alkenyl,
C_{6-14} arylcarbonylarylC_{1-20}alkyl,
C_{2-20}alkenylC_{1-20}alkyl,

C_{6-14} arylC_{2-20}alkenyl, or
heteroarylC_{2-20}alkenyl;

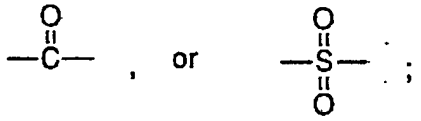
R^4 is

H,
C_{1-20} alkyl,
C_{5-14} aryl, or
heteroaryl;

R^5 can be the same or different when x is greater than 1 and is:

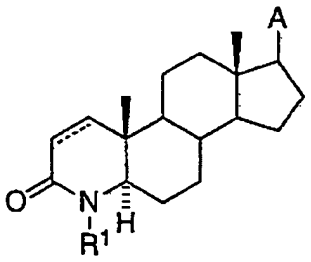
H, or
C_{1-20} alkyl;

W is



x is an integer from 1 to 25.

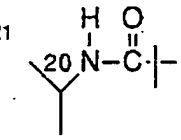
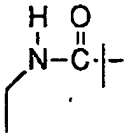
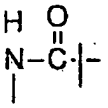
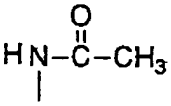
Compounds of the formula

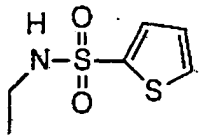


and listed in Table 1 are representative of the compounds claimed in the instant invention. In a preferred embodiment, R^1 may be H or CH_3 and A may be as indicated in Table 1. Particular representative chemical names are also listed in Table 1 adjacent to the respective side chain and

specifically reflect whether the 1 position is saturated or unsaturated. Advantageously, R^1 is CH_3, A is as indicated in Table 1 and the 1 position is saturated. Unless otherwise indicated, the 17-position substituent is assumed to be in the beta configuration.

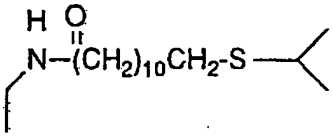
TABLE 1

	Side Chain A	Compound(s):
(1)		4-methyl-20(trimethylacetamido)-5α-4-aza-pregnan-3-one 4-methyl-20(trimethylacetamido)-5α-4-aza-1-pregnen-3-one
(2)		4-methyl-17β(trimethylacetamidomethyl)-4-aza 5α-androst-1-en-3-one 4-methyl-17β(trimethylacetamidomethyl)-4-aza 5α-androstan-3-one
(3)		4-methyl-17β(trimethylacetamido)-4-aza 5α-androst-1-en-3-one 4-methyl-17β(trimethylacetamido)-4-aza 5α-androstan-3-one
(4)		17β(tacetamido)-4-methyl-4-aza 5α-androst-1-en-3-one 17β(acetamido)-4-methyl-4-aza 5α-androstan-3-one

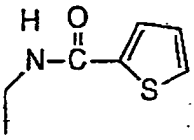
(5) 

4-methyl-17β(2-thiophenesulfonamidomethyl)-4-aza-5α-androst-1-en-3-one

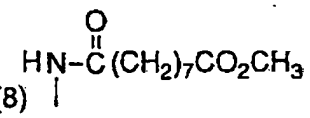
4-methyl-17β(2-thiophenesulfonamidomethyl)-4-aza-5α-androstan-3-one

(6) 

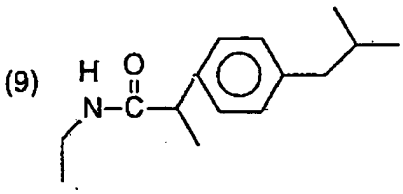
17βisopropylthiododecanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one
17β(isopropylthiododecanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

(7) 

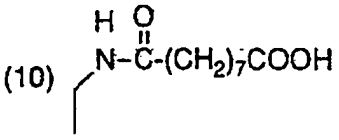
4-methyl-17β(2–(thiophenecarboxamido-methyl)-4-aza-5α-androst-1-en-3-one
4-methyl-17β(thiophenecarboxamido-methyl)-4-aza-5α-androstan-3-one

(8) 

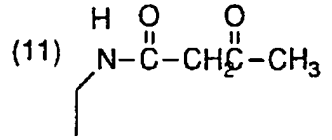
17β(carbomethoxyoctanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one
17β(carbomethoxyoctanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

(9) 

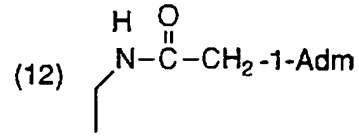
17β((2-(4-isobutylphenyl)-propionamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one
17β((2-(4-isobutylphenyl)-propionamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

(10) 

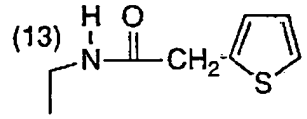
17β(8-carboxyoctanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one
17β(8-carboxyoctanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

(11) 

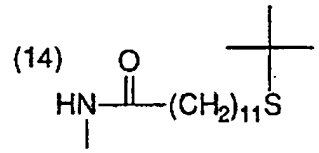
17β(2–(acetoacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one
17β(2–(acetoacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

(12) 

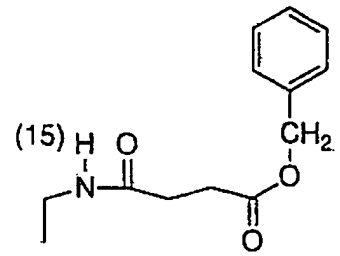
17β(1-Adamantylacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one
17β(1-Adamantylacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

(13) 

4-methyl-17β(2-thiopheneacetamidomethyl)-4-aza-5α-androstane-3-one
4-methyl-17β(2-thiopheneacetamidomethyl)-4-aza-5α-androstane-1-en-3-one

(14) 

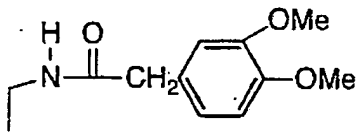
17β(12-(t-butylthio)dodecanoylamido)-4-methyl-4-aza-5α-androstan-3-one
17β(12-(t-butylthio)dodecanoylamido)-4-methyl-4-aza-5α-androstan-1-en-3-one

(15) 

17β(3-(carbobenzoyloxy)propionamido-methyl)-4-methyl-4-aza-5α-androstan-3-one

17β(3-(carbobenzoyloxy)propionamido-methyl)-4-methyl-4-aza-5α-androstan-1-en-3-one

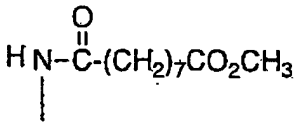
(16)



17β(3,4-dimethoxyphenylacetamido-methyl)-4-methyl-4-aza-5α-androstan-3-one

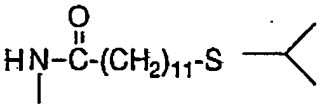
17β(3,4-dimethoxyphenylacetamido-methyl)-4-methyl-4-aza-5α-androstan-1-en-3-one

(17)



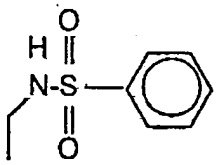
17β(8-(carbomethoxy)octanoylamido)-4-methyl-4-aza-5α-androst-1-en-3-one
17β(8-(carbomethoxy)octanoylamido)-4-methyl-4-aza-5α-androstan-3-one

(18)

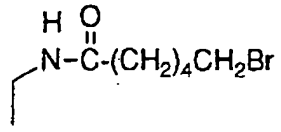


17β(12-isopropylthio)dodecanoylamido)-4-methyl-4-aza-5α-androst-1-en-3-one
17β(12-isopropylthio)dodecanoylamido)-4-methyl-4-aza-5α-androstan-3-one

(19)

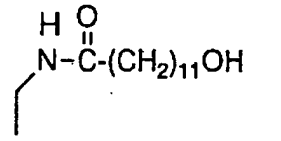


17β(benzenesulfonamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one
17β(benzenesulfonamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

(20) 

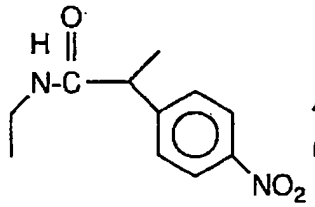
17β(6-Bromohexanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one

17β(6-Bromohexanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

(21) 

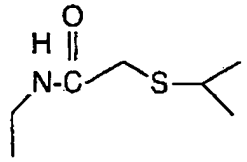
17β(12-hydroxydodecanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one

17β(12-hydroxydodecanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

(22) 

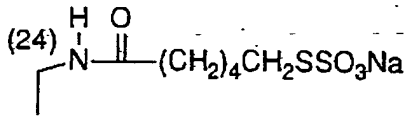
4-methyl-17β(2-(4-nitrophenyl)propionamido-methyl)-4-aza-5α-androst-1-en-3-one

4-methyl-17β(2-(4-nitrophenyl)propionamido-methyl)-4-aza-5α-androstan-3-one

(23) 

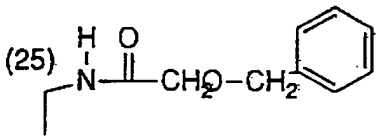
17β(isopropylthioacetamidomethyl)-4-methyl-4-aza5α-androst-1-en-3-one

17β(isopropylthioacetamidomethyl)-4-methyl-4-aza5α-androstan-3-one

(24) 

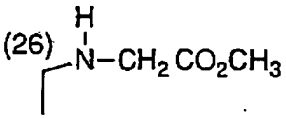
4-methyl-17β(6-thiosulfato)hexanoyl-amidomethyl)-4-aza-5α-androstan-3-one

4-methyl-17β(6-thiosulfato)hexanoyl-amidomethyl)-4-aza-5α-androstan-1-en-3-one

(25) 

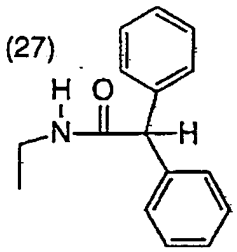
17β(benzoyloxyacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

17β(benzoyloxyacetamidomethyl)-4-methyl-4-aza-5α-androstan-1-en-3-one

(26) 

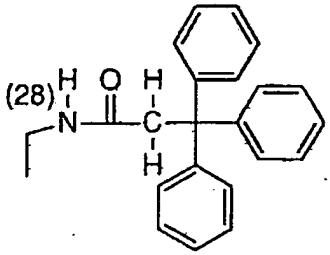
17β(carbomethoxyacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

17β(carbomethoxyacetamidomethyl)-4-methyl-4-aza-5α-androstan-1-en-3-one

(27) 

17β(diphenylacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one

17β(diphenylacetamidomethyl)-4-methyl-4-aza-5α-androstan-1-en-3-one

(28) 

4-methyl-17β(3,3,3-triphenypropion-amidomethyl)-4-aza-5α-androstan-3-one

4-methyl-17β(3,3,3-triphenypropion-amidomethyl)-4-aza-5α-androstan-1-en-3-one

The following additional compounds may also be prepared according to the procedures described in the instant specification. Unless otherwise specified herein, the 17-substituent is presumed to be in the beta configuration.

17ß-(2-Furylacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;
17ß-(4-Isopropylphenylacetamidomethyl)-4-methyl- 4-aza-5α-androstan-3-one;
17ß-(Cyclohexylacetamidomethyl)-4-methyl-4-aza- 5α-androstan-3-one;
17ß-(3-Indolylacetamidomethyl)-4-methyl-4-aza- 5α-androstan-3-one;
4-Methyl-17ß-(4-methylcyclohexanecarboxamidomethyl)-4-aza-5α-androstan-3-one;
17ß-(4-(3-Indolyl)-butyramidomethyl)-4-methyl-4-aza- 5α-androstan-3-one;
17ß-(4-Isobutylbenzamidomethyl)-4-methyl-4-aza-5α- androstan-3-one;
17ß-(Acetoxyacetamidomethyl)-4-methyl-4-aza-5α- androstan-3-one;
17ß-(6-Bromohexanoylamidomethyl)-4-methyl-4-aza-5α- androstan-3-one;
4-Methyl-20-(4-nitrobenzamidomethyl)-4-aza-5α- pregnan-3-one;
20-((3-Acetamido)benzamido)-4-methyl-4-aza-5α- pregnan-3-one;
20-(3,4-Dimethoxyphenylacetamidomethyl)4-methyl- 4-aza-5α-pregnan-3-one;
17ß-(4-Ethoxybenzamidomethyl)-4-methyl-4-aza-5α- androstan-3-one;
4-Methyl-20-(palmitoylamidomethyl)-4-aza-5α- pregnan-3-one;
17ß-(Iminodibenzyl-5-carboxamidomethyl)-4-methyl- 4-aza-5α-androstan-3-one;
4-Methyl-20-(stearoylamido)-4-aza-5α-pregnan-3-one; 4-Methyl-17ß-(3,5-bis-(trifluoromethyl)benzamidomethyl)-4-aza-5α-androstan-3-one;
17ß-(3-Cyanobenzamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;
20-(Heptafluorobutyramidomethyl)-4-Methyl-4-aza-5α-pregnan-3-one;
20-(4-Benzoylbenzamidomethyl)-4-methyl-4-aza-5α-pregnan-3-one;
17ß-(Benztriazol-5-carboxamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;
20-(3,5-Difluorobenzamido)-4-methyl-4-aza-5α-pregnan-3-one;

17ß-(Bis-(4-isopropyl)phenyl)acetamidomethyl-4-methyl-4-aza-5α-androstan-3-one;
4-Methyl-20-(Salicylamidomethyl)-4-aza-5α-pregnan-3-one;
17ß-(Cinnamoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;
17ß-((3-Hydroxy-4,4,4-trichlorobutyramido)methyl)-4-methyl-4-aza-5α-androstan-3-one;
17-Benzoylamido-5-α-4-methyl-4-azaandrostan-3-one;
17-(2-Thiophenesulfonamido)-5-α-4-methyl-4-azaandrostan-3-one:
4-Methyl-17-(phenylthioacetamido)-5-α-4-methyl-4-azaandrostan-3-one;
4-Methyl-17-(4-methylpentanoylamido)-5-α-4-azaandrostan-3-one;
4-Methyl-17-(3-thenoylamino)-5-α-4-azaandrostan-3-one;
17-(3-(4'-Fluoro-3,5,3'-trimethylbiphen-2-yl)propionamido)-4-methyl-5-α-4-azaan-drostan-3-one;
17-(6-(Diethylphosphono)hexanoylamino)-4-methyl-5-α-4-azaandrostan-3-one;
17-((t-Butylthio)acetamido)-4-methyl-5-α-4-azaandrostan-3-one;
4-Methyl-17-(3-thiophenacetamido)-5-α-4-azaandrostan-3-one;
4-Methyl-17-(4-nitrobenzamido)-5-α-4-azaandrostan-3-one;
4-Methyl-17-(3-nitrobenzamido)-5-α-4-azaandrostan-3-one;
17-(2-Fluorobenzamido)-4-methyl-5-α-4-azaandrostan-3-one;
17-(4-cyanobenzamido)-4-methyl-5-α-4-zazaandrostan-3-one;
17-(Benzthiophen-3-ylacetamido)-4-methyl-5-α-4-azaandrostan-3-one;
4-Methyl-17-(2-thiophenecarboxamido)-5-α-4-azaandrostan-3-one;
17-(1-Methyl-2-pyrrolecarboxamido)-4-methyl-5-α-4-azaandrostan-3-one;
17-(4-Carboxy-4methylpentanoylamido)-4-methyl-5-α-4-azaandrostan-3-one;
17-(4-Carbomethoxy-4-methylpentanoylamido)-4-methyl-5-α-4-azaandrostan-3-one;
17-(4-Carbomethoxy-3,3-dimethylbutyroylamido)-4-methyl-5-α-4-azaandrostan-3-one;
4-Methyl-17-(3-phenylbutyroylamido)-5-α-4-azaandrostan-3-one;
17-(2,3-Difluorobenzoylamido)-4-methyl-5-α-4-azaandrostan-3-one:
4-Methyl-17-(2-methylbenzoylamido)-5-α-4-azaandrostan-3-one;

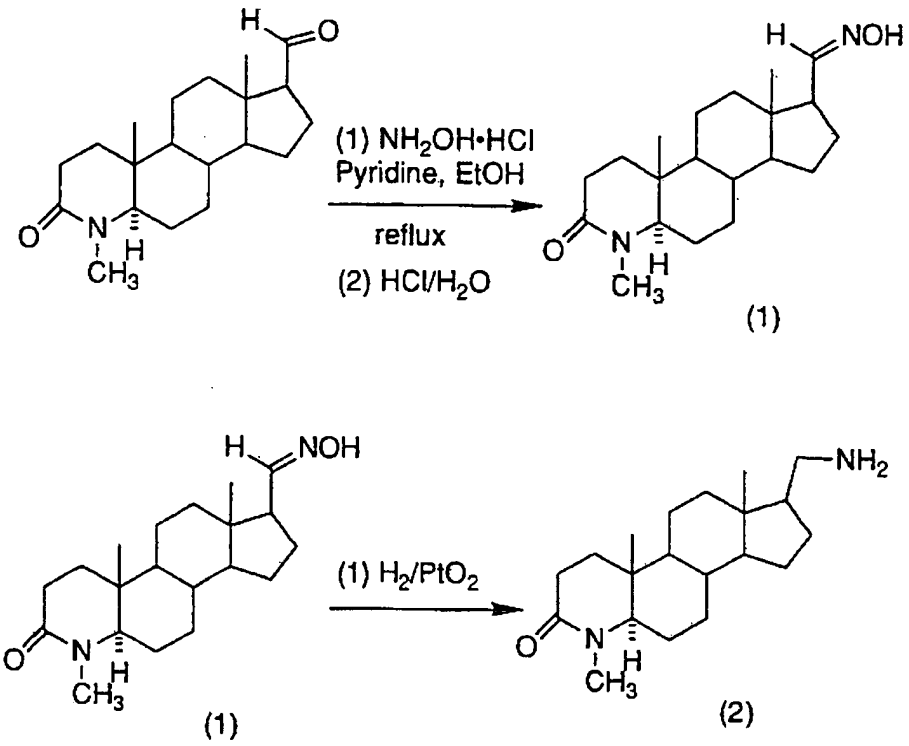
17-(2,3-Dimethylbenzamido)-4-methyl-5-α-4-azaandrostan-3-one;
17-Cinnamoylamido-4-methyl-5-α-4-azaandrostan-3-one;
17-(3,3-Dimethylacrylamido)-4-methyl-5-α-4-azaandrostan-3-one;
17-(3,4-Dimethoxybenzamido)-4-methyl-5-α-4-azaandrostan-3-one;
17-(Acetoxylacetamido)-4-methyl-5-α-4-azaandrostan-3-one;
4-Methyl-17-(4-(2-nitrophenoxy)-butyroylamido)-5-α-4-azaandrostan-3-one;
17-Isobutyroylamido-4-methyl-5-α-4-zazaandrostan-3-one;
17-(3,3-Dimethyl-4-(1-(4-isobutylphenyl)ethoxy)benzamido)-4-methyl-5-α-4-aza--androstan-3-one;
17-(4-Benzyloxybenzamido)-methyl-5-α-4-azaandrostan-3-one;
4-Methyl-17-(3-fluoro-2-methylbenzamido)-5-α-4-azaandrostan-3-one;
4-Methyl-17-(3,5,5,-trimethylhexanoylamino)-5-α-4-azaandrostan-3-one;
17-((Benzylthio)acetamido)-4-methyl-5-α-4-azaandrostan-3-one;
17-(2-Acetoxyisobutyramido)-4-methyl-5-α-4-azaandrostan-3-one;
4-Methyl-17-trifluoroacetamido-5-α-4-azaandrostan-3-one;
17-(2-Hydroxyisobutyramido)-4-methyl-5-α-4-azaandrostan-3-one;
17-(Isonicotinoylamino)-4-methyl-5-α-4-azaandrostan-3-one;
17-(t-Butylacetamido)-4-methyl-5-α-4-azaandrostan-3-one;
4-Methyl-17-phenylacetamido-5-α-4-azaandrostan-3-one;
4-Methyl-17-(picolinoylamido)-5-α-4-azaandrostan-3-one;
4-Methyl-17-(nicotinoylamido)-5-α-4-azaandrostan-3-one;
17-(3-((3-Benzamido)phenyl)propionamido)-4-methyl-5-α-4-azaandrostan-3-one;
17-Formamido-4-methyl-5-α-4-azaandrostan-3-one;
17-(2-(Carbomethoxy)-1-cyclopentenylcarboxamido)-4-methyl-5-α-4-azaandrostan-3-one;
17-(2,6-Difluorobenzamido)-4-methyl-5-α-4-azaandrostan-3-one;
17-(2,6-Dichlorobenzamidomethyl)-5-α-4-methyl-4-azaandrosatan-3-one;
17-(3-Nitrobenzoylamidomethyl)-5-α-4-methyl-4-azaandrostan-3-one;
17-(4-Nitrobenzoylamidomethyl)-5-α-4-methyl-4-azaandrostan-3-one;
17-(3,3-Diphenylpropionamidomethyl)-5-α-4-methyl-4-azaandrostan-3-one;

17-((3-(Iminodibenz-5-ylmethyl)benzoyl)aminomethyl)-4-methyl-5-α-4-azaandrostan-3-one;
17-(3-Hydroxy-4,4,4,-trichlorobutyroylamidomethyl))-5-α-4-methyl-4-azaandrostan-3-one;
17-Formamidomethyl-5-α-4-methyl-4-azaandrostan-3-one;
4-Methyl-17-(3,3,3,-triphenylpropionamidomethyl)-5-α-4-azaandrostan-3-one;
20-((Isopropylthio)acetamido)-4-methyl-5-α-4-azapregnan-3-one;
20-((Isopropylthio)acetamido)-5-α-4-azapregnan-3-one;
4-Methyl-17-((phenylthio)acetamidomethyl)-5-α-4-azaandrostan-3-one;
17-((t-Butylthio)acetamidomethyl)-5-α-4-methyl-4-azaandrostan-3-one;
17-(3-Methyl-2-thenoylaminomethyl)-4-methyl-5-α-4-azaandrostan-3-one;
17-(5-Methyl-2-thenoylaminomethyl)-4-methyl-5-α-4-azaandrostan-3-one;
4-Methyl-17-(3-(trifluoromethyl)-benzamidomethyl)-5-α-4-azaandrostan-3-one;
17-Benzamidomethyl-4-methyl-5-α-4-azaandrostan-3-one or
17-(2,3-Difluorobenzamido)-4,7-dimethyl-5-α-4-azaandrostan-3-one.

Also included herein are the 4-N-H (or 4-N-CH_3 if the 4-N-H is specified) analogs of the above specified compounds.

Synthesis of Testosterone 5-α Reductase Inhibitors:

Scheme 1 illustrates the synthesis of the intermediate oximes and amines used to produce compounds claimed in the instant invention.



SCHEME I

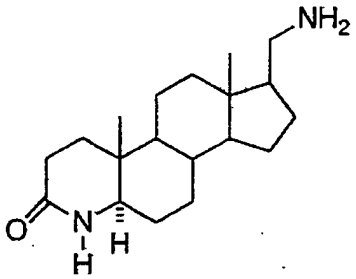
A stirred mixture of 4-methyl-3-oxo-5-α-4-azaandrostan-17-carboxaldehyde, hydroxylamine hydrochloride, anhydrous pyridine, and anhydrous ethanol is refluxed gently under a nitrogen atomosphere for six to seven hours. After cooling, the ice-cooled mixture is diluted, with stirring, with a slight excess of chilled dilute hydrochloric acid. The suspension is then aged for about twenty minutes, filtered, washed with water and dried to give compound 1.

A mixture of the oxime (1), ethanol, glacial acetic acid and water is reduced in the presence of platinum oxide (PtO_2) until chromatographic analysis (TLC) indicates complete reduction to the amine (2). The filtered reaction mixture is concentrated in vacuo; the resultant residue is dissolved in chloroform ($CHCl_3$) and washed with fresh dilute sodium hydrogen carbonate solution.

The chloroform phase is then dried with sodium sulfate (Na_2SO_4). Concentration of the resultant $CHCl_3$ solution followed by trituration of the residue with hexane/ether will yield 2 as a white solid.

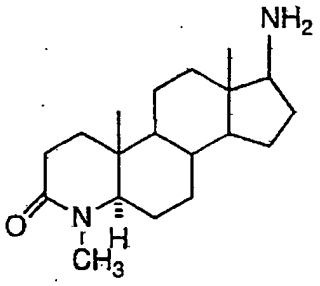
The following amines are representative of those obtained from the corresponding carbonyl compounds utilizing the basic procedures described in Scheme 1 for preparation of the oximes and amines:

3)



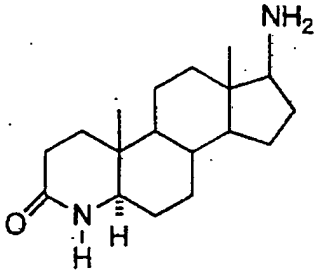
17-Aminomethyl-5-α-4-azaandrostan-3-one;

4)



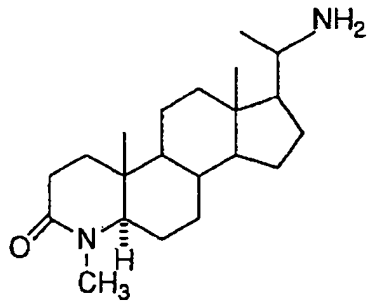
17-Amino-4-methyl-5-α-4-azaandrostan-3-one;

5)



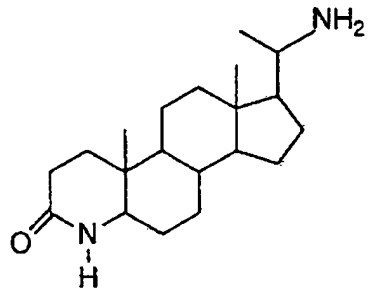
17-Amino-5-α-4-azaandrostan-3-one;

6)



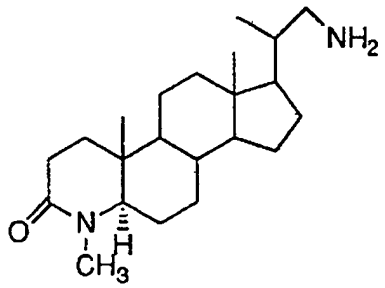
20-Amino-4-methyl-5-α-4-azapregnan-3-one;

7)



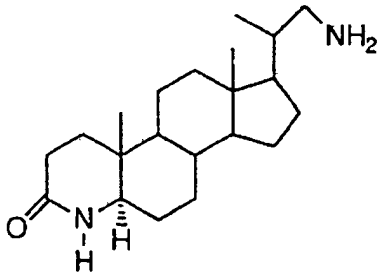
20-Amino-5-α-4-azapregnan-3-one;

8)



20-(Aminomethyl)-4-methyl-5-α-4-azapregnan-3-one;

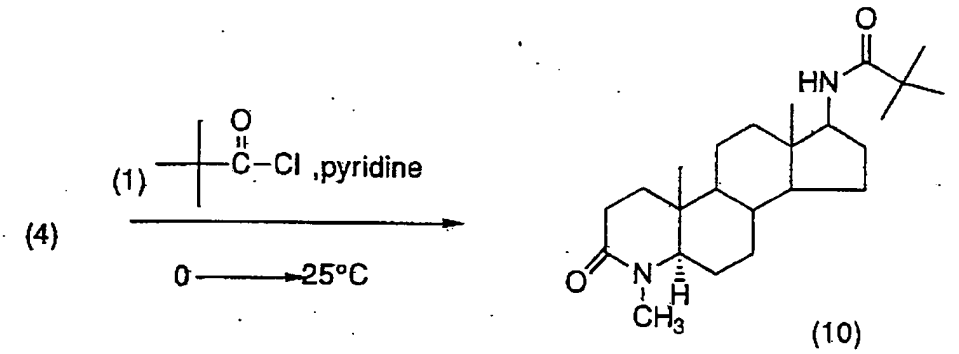
9)



20-(Aminomethyl)-5-α-4-azapregnan-3-one;

As Scheme 1 indicates, the oximes useful as intermediates may readily be prepared by reacting a 4-azasteroidal aldehyde or ketone with hydroxylamine hydrochloride to form the corresponding oxime. The resultant oximes are subsequently reduced with hydrogen (H_2) and platinum oxide (PtO_2) or other suitable reducing agent to yield the respective amine. The product amides may be further alkylated with, for example, alkyl halides to give the corresponding R^2 alkylated compounds. Alternatively, the primary amines may be alkylated by well known synthetic procedures to the corresponding secondary amines and then acylated to the product amides.

Scheme 2 illustrates the synthesis of the compound 4-methyl-17(trimethylacetylamido)-5-α-4 azaandrostan-3-one and is representative of a basic synthesis of compounds claimed in the instant invention in which an amine is reacted with an acylating agent (or acid equivalent). These reagents include acyl halides and acid anhydrides.

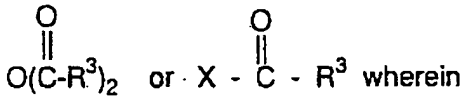


SCHEME 2

To a stirred, ice-cold solution of IV, anhydrous methylene chloride and pyridine is added trimethylacetylchloride dropwise over approximately one minute under a nitrogen atmosphere. After an additional fifteen minutes at ice-bath temperatures, the mixture is allowed to warm to room temperature (25°C) and stirred for an additional fourteen hours. The mixture is then transferred to a separatory funnel with additional CH_2Cl_2, washed with dilute (0.3N)

HCl, dried (Na_2SO_4), concentrated and recrystallized (ethyl acetate) to yield 10 as a white solid.

As Scheme 2 illustrates, 4-azasteroidal primary or secondary amines described in the instant invention are reacted with the desired activated carbonyl compound, such as trimethylacetyl chloride, to yield the target amide. Representative acyl halides or acid anhydrides of the formula:



R^3 may generally be:

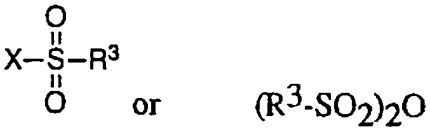
C_{1-20}alkyl,
aryl,
heteroaryl,
arylC_{1-20}alkyl,
heteroarylC_{1-20}alkyl,
C_{1-20}alkylarylC_{1-20}alkyl,
C_{1-20}alkyloxycarbonylalkyl,
C_{1-20}alkylcarbonylC_{1-20}alkyl,
C_{1-20}cycloalkylC_{1-20}alkyl,
arylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
haloC_{1-20}alkyl,
arylC_{1-20}alkyloxyC_{1-20}alkyl,
diarylC_{1-20}alkyl,
triarylC_{1-20}alkyl,
C_{2-20} alkenyl,
C_{2-20} alkenylC_{1-20}alkyl,
C_{2-20}alkynylC_{1-20}alkyl,
arylC_{2-20}alkynylC_{1-20}alkyl,
heteroarylC_{2-20}alkylnylC_{1-20}alkyl,
or arylC_{2-20}alkenyl may be used in the instant invention.

R^3 is also as specifically described in the examples section of the present application. R^3 may be, for example, t-butyl; 2,2-diphenylethyl,3-thienyl, 2-thienyl, -11-(isopropylthio)undecyl, -7-(carbomethoxy)heptyl, 1-(1-(4-isobutylphenyl-)ethyl, -7-(carboxy)heptyl, -acetylmethyl, -1-adamantylmethyl, -2-thienylmethyl, -2-(carbobenzyloxy)ethyl, -3,4-dimethoxyphenyl, -phenyl, -5-bromopentyl, phenylthiomethyl, -t-butylthiomethyl, -3-methyl-2-thienyl, 5-methyl-2-thienyl, -11-hydroxyundecyl, -1-(4-nitrophenyl)ethyl, -isopropylthiomethyl, 5-(thiosulfato)pentyl,-benzyloxymethyl, carbomethoxymethyl, diphenylmethyl, triphenylmethyl, -2-furyl, 4-isopropylphenyl, cyclohexylmethyl, 4-methylcyclohexyl, 3-(3-indolyl)propyl, 3-Indolylmethyl, 4-isobutylphenyl, 4-nitrophenyl, 3-nitrophenyl, 3-acetamidomethyl, 4-ethoxyphenyl, hexadecyl, stearyl, 3,5-Bis(trifluoromethyl)benzyl, 3-cyanophenyl, heptafluoropropyl, 4-benzoylphenyl, 5-benztriazolyl, 3,5-difourophenyl, bis(4-isopropylphenyl)methyl, 2-hydroxyphenyl, phenylvinyl, 2-hydroxy-3,3,3-trichloropropyl, methyl, allyl, n-propyl, n-octyl, isopropyl, (isopropylthio)methyl, isobutyl, ethyl; 2,2,2-triphenylethyl, benzyl, octadecyl, 2(ethyl)phenyl, 3(chloro)phenyl, 4(methyl)phenyl, 2,3(dichloro)phenyl, 2,6(dichloro)phenyl, 4(fluoro)phenyl, 3(methoxy)phenyl, 3-(acetamido)phenyl, 3-(Iminodibenz-5-ylmethyl)phenyl, 3-trifluoromethylphenyl, 2(ethoxy)phenyl, formyl, 2-napthyl, or 2-thiazolyl. Each of the acid chlorides having the above R^3 groups are readily available from, for example, Aldrich Chemical Company or may readily be prepared from the corresponding acid.

Acyl halides or activated carbonyl compounds disclosed in this invention are commercially available or may be prepared from the corresponding carboxylic acid and thionyl chloride ($SOCl_2$), phosphorous pentahalide (PX_5), or phosphorous trihalide (PX_3). See Ansell in Patai, "The Chemistry of Acyl Halides", 35-48, Interscience, New York (1972).

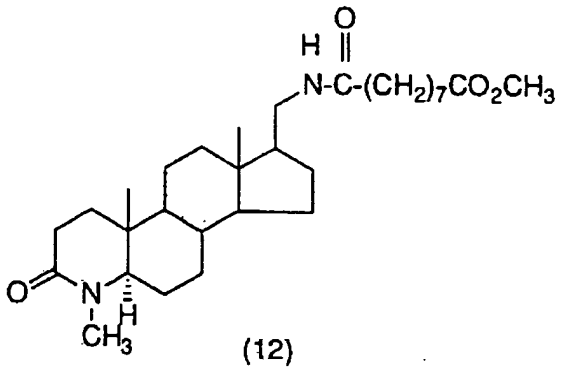
The primary or secondary amines disclosed in the instant invention may also be reacted with alkyl and aryl sulfonyl halides or anhydrides to yield compounds claimed in the instant invention.

If a sulfonylhalide or anhydride of the formula



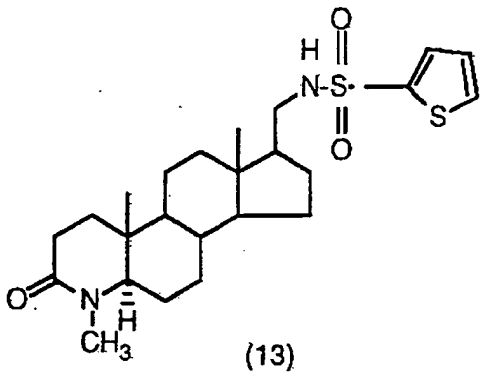
is used, R^3 may equal the groups defined above for the carbonyl species.

Amides or sulfonamides representative of those obtained from the corresponding amines utilizing the basic procedure described in Scheme 2 by substituting either the amine or the activated carbonyl compound may be prepared. For example, compound 6 may be substituted for compound 4 in Scheme 2 and reacted with the indicated acylating agent (trimethylacetyl chloride) to yield compound 11 (4-methyl-20-(trimethylacetamido)-5-α-4-azapregnan-3-one). If compound 2 is reacted with 8-(carbomethoxy)octanoyl chloride using the procedure described in Scheme 2, (17-(8-(Carbomethoxy)-octanoylamidomethyl)-4-methyl-5-α-4-aza-androstan-3-one) is produced:



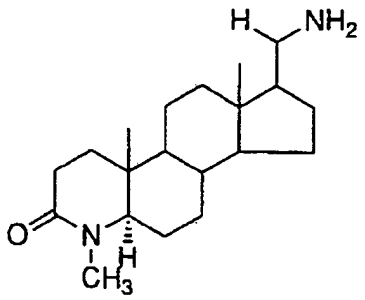
(12)

If a sulfonyl halide, for example, thiophene-2-sulfonylchloride, is substituted for an acyl halide and reacted with an amine such as 2, (4-methyl-17-(2-thiophenesulfonylamidomethyl)-5-α-4-azaandrostan-4-one) may be prepared:

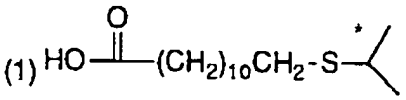


(13)

Scheme 3 illustrates the synthesis of 17ß-(12-(Isopropylthio)dodecanoylamidomethyl)-4-methyl-5α-aza-androstan -3-one (14):

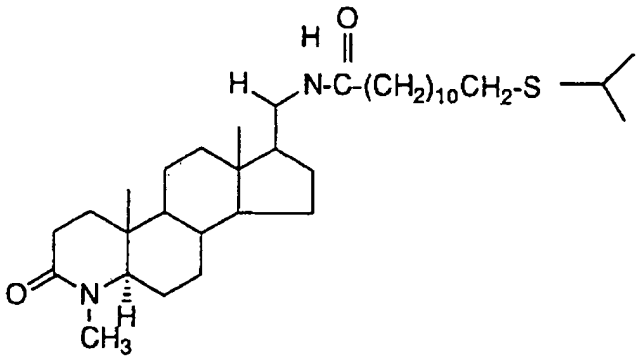


2

(1) 

(2) 4-dimethylaminopyridine (DMAP)

(3) N,N'-dicyclohexylcarbodi-imide (DCC)



14

(* prepared from 12-bromododecanoic acid and sodium isopropylthiolate)

SCHEME 3

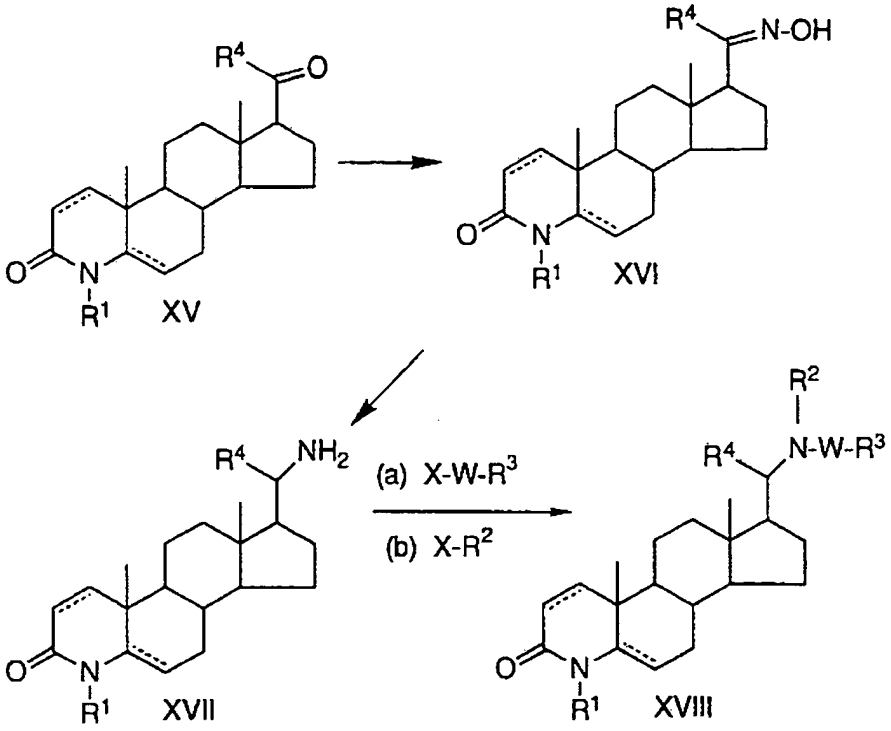
DCC is a well known coupling reagent used in peptide synthesis to generate amide bonds from a free acid and an amine. Coupling reagents

may generally be used when the free acid is readily available or when the alternative acid halide is internally labile (e.g., when a thio group is present). An intermediate anhydride of the acid is generated which futher reacts with the amine. In Scheme 3, 12-(isopropylthio)-dodecanoic acid is reacted with 2, DCC, and DMAP to produce the corresponding amide (14). For example, DCC is used when R^3 is C_{1-20}alkylthioC_{1-20}alkyl or hydroxylC_{1-20}alkyl.

Additionally, dehydrogenation of the 1,2 position or the 5,6 position may readily be accomplished by known synthetic methodology to produce the claimed 1-en or 5-en derivatives. See U.S. 5,061,802; Dolling et al., JACS, 110, 3318-19 (1988).

Schemes 4, 5 and 6 further illustrate how compounds claimed in the instant invention may be prepared. In Scheme 4, the staring 4-azasteroid aldehyde or ketone (XV), obtained by known synthetic methods, is reacted to form the oxime (XVI); reduced to the amine (XVII) and reacted with an activated carbonyl or sulfonyl compound and, optionally, an alkylhalide (X-R^2) to form XVIII. Of

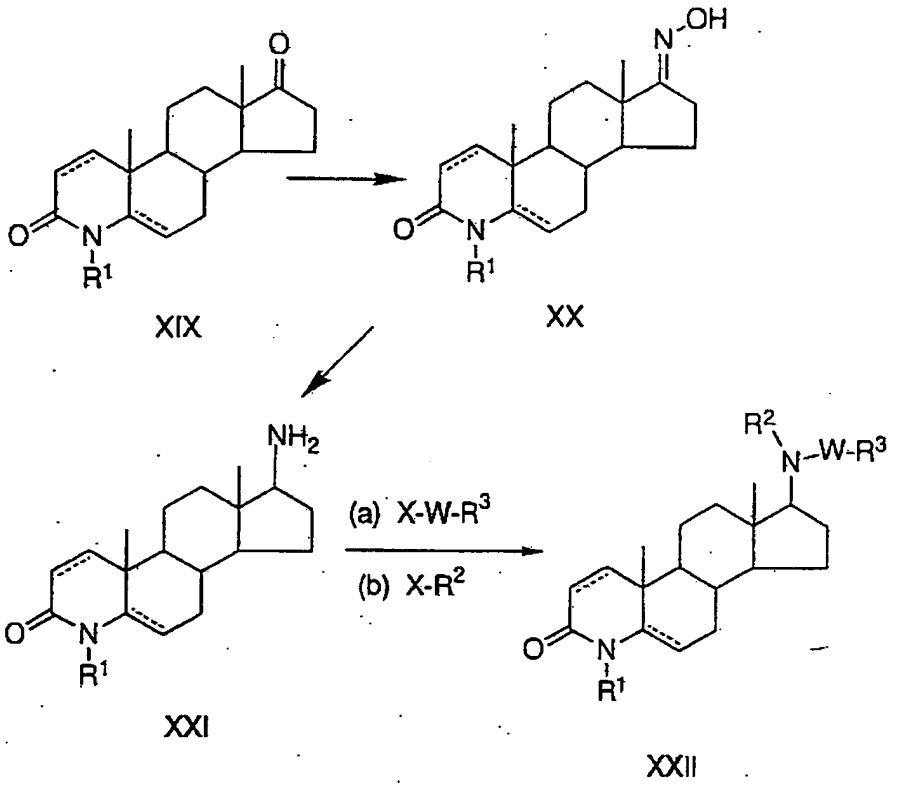
course, if the optional alkyl halide is not utilized, R^2 on XVIII is H.



Scheme 4

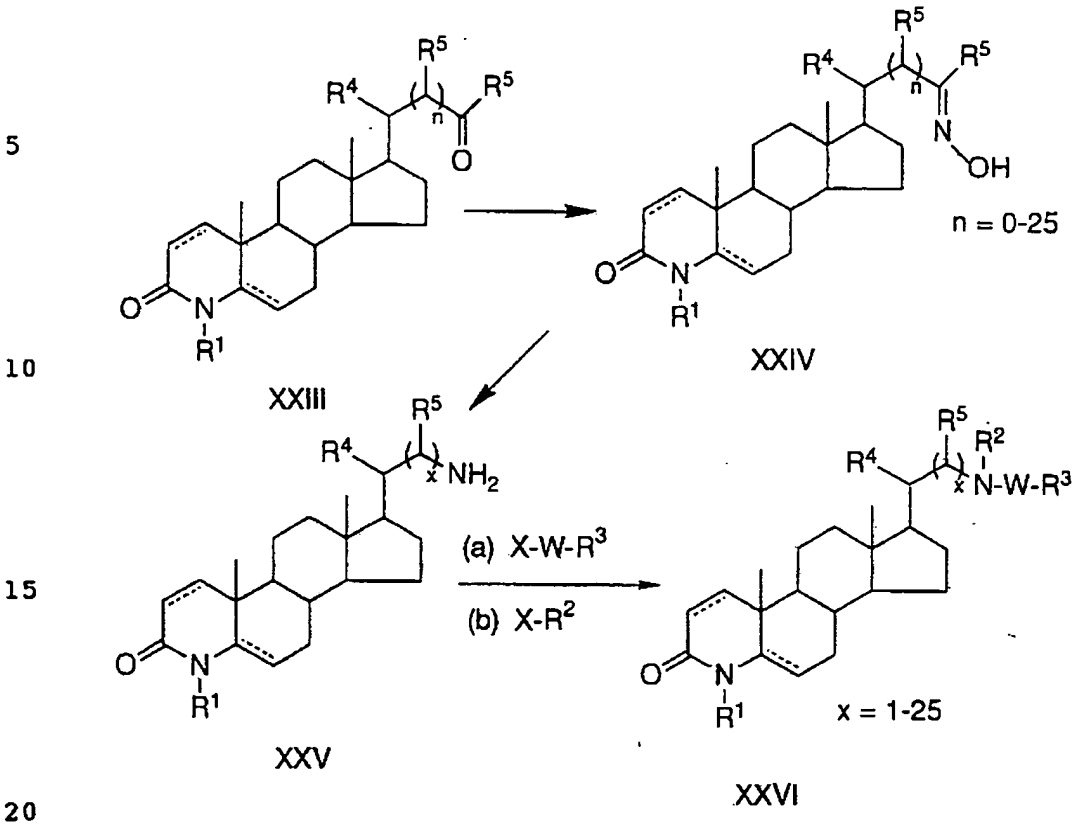
In Scheme 5, the identical procedure is followed using a generic 4-azasteroid (XIX) prepared by known synthetic methods to produce the oxime (XX) which is reduced to the amine (XXI) and reacted with an

activated carbonyl or sulfonyl compound (X-W-R^3) to yield (XXII).



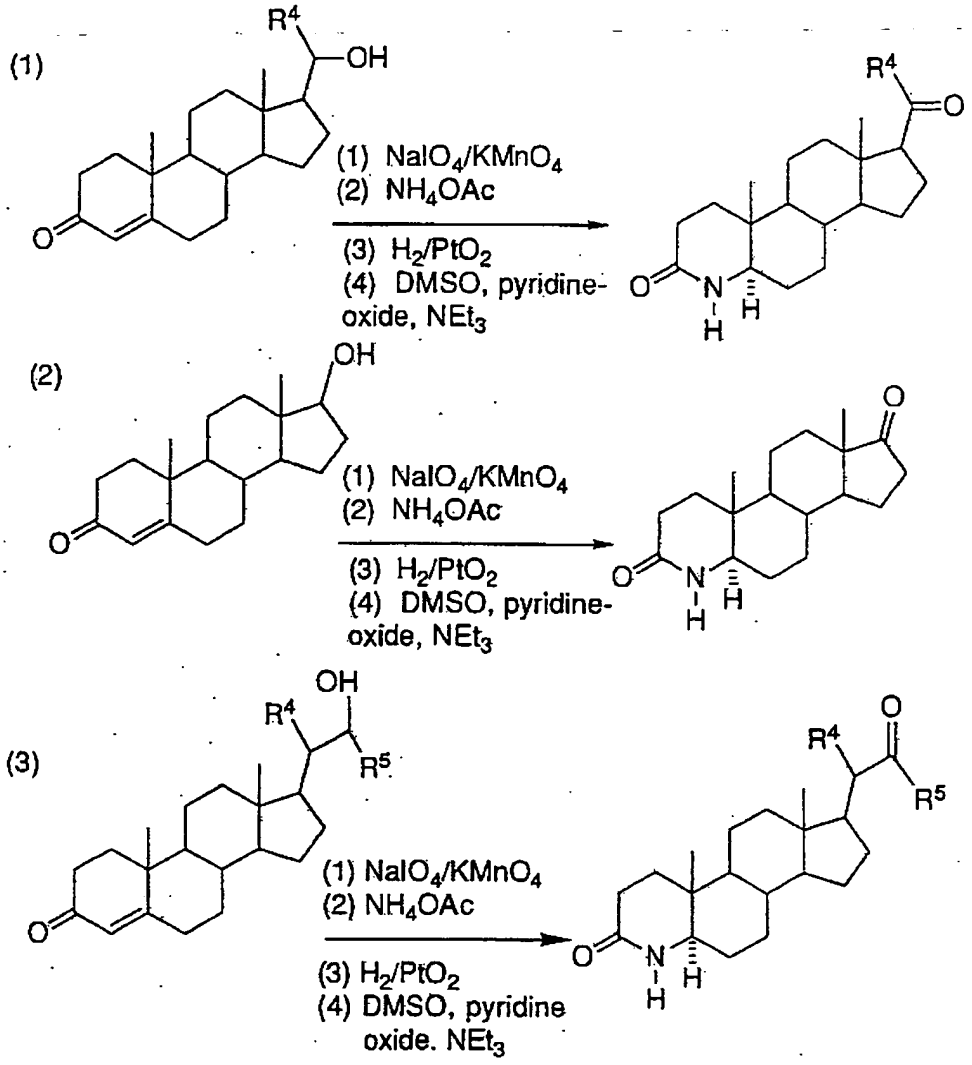
Scheme 5

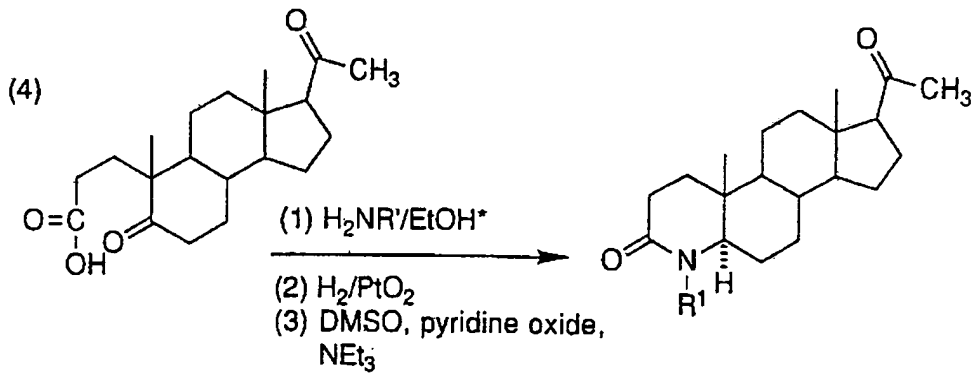
In Scheme 6, the generic 4-azasteroid XXIII, also obtained from well known synthetic methodology, is reacted to form the oxime XXIV which is further reduced to form XXV and subsequently reacted with an activated carbonyl or sulfonyl compound to form XXVI.



SCHEME 6

The starting 4-azasteroidal ketones used in the present invention may be prepared according to the well known basic procedures described in Scheme 7.


(1)
R4
OH
O
(1) NaIO4/KMnO4
(2) NH4OAc
(3) H2/PtO2
(4) DMSO, pyridine-oxide, NEt3
R4
O
O
N
H
H
(2)
OH
O
(1) NaIO4/KMnO4
(2) NH4OAc
(3) H2/PtO2
(4) DMSO, pyridine-oxide, NEt3
O
O
N
H
H
(3)
OH
R4
R5
O
(1) NaIO4/KMnO4
(2) NH4OAc
(3) H2/PtO2
(4) DMSO, pyridine oxide. NEt3
R4
O
R5
O
N
H
H



* U. S. Pat. No. 4,377,584

Scheme 7

The following examples further describe the synthesis of compounds claimed in the instant invention.

Synthesis of Starting -4-azasteroid oximes:

EXAMPLE 1

1) 4-Methyl-3-oxo-5-α-4-azaandrostan-17-carboxaldehyde oxime

A stirred mixture of 4-methyl-3-oxo-5-a-4-azaandrostan-17-carboxaldehyde (0.952 g, 3.0 mM), hydroxylamine hydrochloride (1.10 g, 15.8 mM), anhydrous pyridine (6 mL), and anhydrous ethanol (12 mL) was refluxed gently under a nitrogen atmosphere for 6.3 hours. After cooling, the ice-cooled mixture was diluted, with stirring, with a slight excess of chilled dilute hydrochloric acid (ca. 0.3 N), the suspension was aged for ca. 20 minutes, filtered,

washed with water and dried to give (1) 0.855 g. MS M^+ calcd for $C_{20}H_{32}H_2O_2$ 332.48. observed m/e 332.

Synthesis of Reactant 4-azasteroid Amines:

EXAMPLES 2-9

2) 17-Aminomethyl-4-methyl-5-α-4-azaandrostan-3-one.

A mixture of (1) (0.67 g,., 2.0 mM), ethanol (100 mL), glacial acetic acid (8 mL) and water (4 mL) was reduced in a hydrogen atmosphere (40 p.s.i.) at room temperature in the presence of PtO_2 until TLC analysis indicated complete reduction. The filtered reaction mixture was concentrated in vacuo, the residue taken up in chloroform, and the chloroform solution washed with fresh dilute sodium hydrogen carbonate solution and dried (Na_2SO_4). Concentration of the filtered chloroform solution followed by trituration of the residue obtained with hexane containing a small amount of ether yielded (2) as an off-white solid. MS MH^+ calcd for $C_{20}H_{34}N_2O$ 318.49, observed m/e 319.

The following amines are representative of those obtained from the corresponding carbonyl compounds utilizing the above procedures:

3) 17-Aminomethyl-5-α-4-azaandrostan-3-one.

4) 17-Amino-4-methyl-5-α-4-azaandrostan-3-one.

5) 17-Amino-5-α-4-azaandrostan-3-one.

6) 20-Amino-4-methyl-5-α-4-azapregnan-3-one.

7) 20-Amino-5-α-4-azapregnan-3-one.

8) 20-(Aminomethyl)-4-methyl-5-α-4-azapregnan-3-one.

9) 20-(Aminomethyl)-5-α-4-azapregnan-3-one.

Synthesis of Amino substituted azasteroids:

EXAMPLES 10-14

10) 4-Methyl-17ß-(trimethylacetamido)-5-α-4-azaandrostan-3-one.

To a stirred, ice-cold solution of (4) (0.091 g, 0.3 mM), anhydrous methylene chloride (5 mL), and pyridine (0.1 mL, 1.2 mM), was added trimethylacetyl chloride (0.05 mL, 0.4 mm) dropwise over ca. one minute (nitrogen atmosphere). After an additional 15 min. at ice-bath temperatures the mixture was allowed to warm to room temperature and stir at ambient temperature overnight. The mixture was then transferred to a separatory funnel with additional methylene chloride, washed with dilute (ca. 0.3N) hydrochloric acid, and dried (Na_2SO_4). Concentration of the filtered solution followed by recrystallization (ethyl acetate) of the residue obtained gave (10) as a white solid. MS M^+ calcd for $C_{24}H_{40}N_2O_2$ 388.59, observed m/e 388.

11) 4-Methyl-20-(trimethylacetamido)-5-α-4-azapregnan-3-one.

When (4) in the above reaction was replaced by (6), (11) was obtained as a white solid. MS M^+ calcd for $C_{26}H_{44}H_2O_2$ 416.65, observed m/e 416.

12) 17ß-(8-(Carbomethoxy)octanoylamidomethyl)-4-methyl-5-α-4-azaandrostan-3-one.

When (2) was reacted with 8-carbomethoxy-octanoyl chloride using the conditions of Example (10), (12) was obtained as a thick oil. MS M^+ calcd for $C_{30}H_{50}N_2O_4$ 502.74, observed m/e 502.

13) 4-Methyl-17ß-(2-thiophenesulfonylamidomethyl)-5-α-4-azaandrostan-3-one.

When the 8-carbomethoxyoctanoyl chloride in the above example was replaced with 2-thiophene- sulfonyl chloride, (13) was obtained as a white solid. MS M^+ calcd for $C_{24}H_{36}N_2O_3S_2$ 464.68, observed m/e 464.

14) 17ß-(12-(Isopropylthio)dodecanoylamidomethyl)-4-methyl-5-α-4-aza-androstan-3-one.

To a stirred solution of (2) (0.028 g, 0.09 mM) and 12-(isopropylthio)dodecanoic acid (0.025 g, 0.09 mM) (prepared from 12-bromododecanoic acid and sodium isopropylthiolate by heating in 1.2-dimeth-oxyethane) in methylene chloride (3 mL) was added 4-(dimethylamino)-pyridine (0.011 g, 0.09 mM) followed by a solution of N,N'-dicyclohexylcarbodiimide (0.020 g, o.097 mM) in a minimum of the same solvent. After stirring for 12-14 hours, the mixture was filtered and the filtrate concentrated in vacuo. Flash chromatography (silica gel, ethyl acetate as eluant) yielded (14) as a very thick oil. MS MH^+ calcd for $C_{35}H_{62}N_2O_2S$ 574.95, observed m/e 575.

Examples 15-38 in the following list are prepared according to the basic procedures described above to further exemplify the invention.

15) 4-Methyl-17ß(trimethylacetamidomethyl)-4-aza-5α-androstan-3-one;

16) 17ß(Acetamido)-4-methyl-4-aza-5α-androstan-3-one;

17) 4-Methyl-17ß(2-thiophenecarboxamidomethyl)-4-aza-5α-androstan-3-one;

18) 17ß(2-(4-Isobutylphenyl)propionamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

19) 17ß(8-Carboxyoctanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

20) 17ß(Acetoacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

21) 17ß(1-Adamantylacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

22) 4-Methyl-17ß(2-thiopheneacetamidomethyl)-4-aza-5α-androstan-3-one;

23) 17ß(12-(t-Butylthio)dodecanoylamido)-4-methyl-4-aza-5α-androstan-3-one;

24) 17ß(3-(Carbobenzyloxy)propionamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

25) 17ß(3,4-Dimethoxyphenylacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

26) 17ß(8-(Carbomethoxy)octanoylamido)-4-methyl-4-aza-5α-androstan-3-one;

27) 17ß(Isopropylthiododecanoylamido)-4-methyl-4-aza-5α-androstan-3-one;

28) 17ß(Benzenesulfonamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

29) 17ß(6-Bromohexanoxylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

30) 17ß(12-Hydroxydodecanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

31) 4-Methyl-17ß(2-(4-nitrophenyl)propionamido-methyl)-4-aza-5α-androstan-3-one,

32) 17ß(Isopropylthioacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

33) 4-Methyl-17ß(6-(thiosulfato)hexanoylamidomethyl)-4-aza-5α-androstan-3-one;

34) 17ß(Benzyloxyacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

35) 17ß(Carbomethoxyacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

36) 17ß(Diphenylacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one;

37) 4-Methyl-17ß(3,3,3-triphenylpropion amidomethyl)-4-aza-5α-androstan-3-one;

38) 4-Methyl-17ß(3-thiophenecarboxamido)-4-aza-5α-androstan-3-one.

In addition to the above compounds, the following compounds were also prepared according to the basic procedures described in the specification:

39) 17-(2,6-Dichlorobenzamidomethyl)-5-α-4-methyl-4-azaandrosatan-3-one.

40) 17-(3-Nitrobenzoylamidomethyl)-5-α-4-methyl-4-azaandrostan-3-one.

41) 17-(4-Nitrobenzoylamidomethyl)-5-α-4-methyl-4-azaandrostan-3-one.

42) 17-(3,3-Diphenylpropionamidomethyl)-5-α-4-methyl-4-azaandrostan-3-one.

43) 17-Benzoylamido-5-α-4-methyl-4-azaandrostan-3-one.

44) 17-(2-Thiophenesulfonamido)-5-α-4-methyl-4-azaandrostan-3-one.

45) 17-((3-(Iminodibenz-5-ylmethyl)benzoyl)aminomethyl)-4-methyl-5-α-4-azaandrostan-3-one.

46) 17-(3-Hydroxy-4,4,4,-trichlorobutyroylamidomethyl))-5-α-4-methyl-4-azaandrostan-3-one.

47) 17-Formamidomethyl-5-α-4-methyl-4-azaandrostan-3-one.

48) 4-Methyl-17-(3,3,3,-triphenylpropionamidomethyl)-5-α-4-azaandrostan-3-one.

49) 4-Methyl-17-(phenylthioacetamido)-5-α-4-methyl-4-azaandrostan-3-one.

50) 4-Methyl-17-(4-methylpentanoylamido)-5-α-4-azaandrostan-3-one.

51) 20-((Isopropylthio)acetamido)-4-methyl-5-α-4-azapregnan-3-one.

52) 20-((Isopropylthio)acetamido)-5-α-4-azapregnan-3-one.

53) 4-Methyl-17-(3-thenoylamino)-5-α-4-azaandrostan-3-one.

54) 4-Methyl-17-((phenylthio)acetamidomethyl)-5-α-4-azaandrostan-3-one.

55) 17-(3-(4'-Fluoro-3,5,3'-trimethylbiphen-2-yl)propionamido)-4-methyl-5-α-4-azaan-drostan-3-one.

56) 17-(6-(Diethylphosphono)hexanoylamino)-4-methyl-5-α-4-azaandrostan-3-one.

57) 17-((t-Butylthio)acetamidomethyl)-5-α-4-methyl-4-azaandrostan-3-one.

58) 17-(3-Methyl-2-thenoylaminomethyl)-4-methyl-5-α-4-azaandrostan-3-one.

59) 17-((t-Butylthio)acetamido)-4-methyl-5-α-4-azaandrostan-3-one.

60) 17-(5-Methyl-2-thenoylaminomethyl)-4-methyl-5-α-4-azaandrostan-3-one.

61) 4-Methyl-17-(3-(trifluoromethyl)-benzamidomethyl)-5-α-4-azaandrostan-3-one.

62) 17-Benzamidomethyl-4-methyl-5-α-4-azaandrostan-3-one.

63) 4-Methyl-17-(3-thiophenacetamido)-5-α-4-azaandrostan-3-one.

64) 4-Methyl-17-(4-nitrobenzamido)-5-α-4-azaandrostan-3-one.

65) 4-Methyl-17-(3-nitrobenzamido)-5-α-4-azaandrostan-3-one.

66) 17-(2-Fluorobenzamido)-4-methyl-5-α-4-azaandrostan-3-one.

67) 17-(4-cyanobenzamido)-4-methyl-5-α-4-zazaandrostan-3-one.

68) 17-(Benzthiophen-3-ylacetamido)-4-methyl-5-α-4-azaandrostan-3-one.

69) 4-Methyl-17-(2-thiophenecarboxamido)-5-α-4-azaandrostan-3-one.

70) 17-(1-Methyl-2-pyrrolecarboxamido)-4-methyl-5-α-4-azaandrostan-3-one.

71) 17-(4-Carboxy-4methylpentanoylamido)-4-methyl-5-α-4-azaandrostan-3-one.

72) 17-(4-Carbomethoxy-4-methylpentanoylamido)-4-methyl-5-α-4-azaandrostan-3-one.

73) 17-(4-Carbomethoxy-3,3-dimethylbutyroylamido)-4-methyl-5-α-4-azaandrostan-3-one.

74) 4-Methyl-17-(3-phenylbutyroylamido)-5-α-4-azaandrostan-3-one.

75) 17-(2,3-Difluorobenzoylamido)-4-methyl-5-α-4-azaandrostan-3-one.

76) 4-Methyl-17-(2-methylbenzoylamido)-5-α-4-azaandrostan-3-one.

77) 17-(2,3-Dimethylbenzamido)-4-methyl-5-α-4-azaandrostan-3-one.

78) 17-Cinnamoylamido-4-methyl-5-α-4-azaandrostan-3-one.

79) 7-(3,3-Dimethylacrylamido)-4-methyl-5-α-4-azaandrostan-3-one.

80) 17-(3,4-Dimethoxybenzamido)-4-methyl-5-α-4-azaandrostan-3-one.

81) 17-(Acetoxylacetamido)-4-methyl-5-α-4-azaandrostan-3-one.

82) 4-Methyl-17-(4-(2-nitrophenoxy)-butyroylamido)-5-α-4-azaandrostan-3-one.

83) 17-Isobutyroylamido-4-methyl-5-α-4-zazaandrostan-3-one.

84) 17-(3,3-Dimethyl-4-(1-(4-isobutylphenyl)ethoxy)benzamido)-4-methyl-5-α-4-aza--androstan-3-one.

85) 17-(4-Benzyloxybenzamido)-methyl-5-α-4-azaandrostan-3-one.

86) 4-Methyl-17-(3-fluoro-2-methylbenzamido)-5-α-4-azaandrostan-3-one.

87) 4-Methyl-17-(3,5,5,-trimethylhexanoylamino)-5-α-4-azaandrostan-3-one.

88) 17-((Benzylthio)acetamido)-4-methyl-5-α-4-azaandrostan-3-one.

89) 17-(2-Acetoxyisobutyramido)-4-methyl-5-α-4-azaandrostan-3-one.

90) 4-Methyl-17-trifluoroacetamido-5-α-4-azaandrostan-3-one.

91) 17-(2-Hydroxyisobutyramido)-4-methyl-5-α-4-azaandrostan-3-one.

92) 17-(Isonicotinoylamino)-4-methyl-5-α-4-azaandrostan-3-one.

93) 17-(t-Butylacetamido)-4-methyl-5-α-4-azaandrostan-3-one.

94) 4-Methyl-17-phenylacetamido-5-α-4-azaandrostan-3-one.

95) 4-Methyl-17-(picolinoylamido)-5-α-4-azaandrostan-3-one.

96) 4-Methyl-17-(nicotinoylamido)-5-α-4-azaandrostan-3-one.

97) 17-(3-((3-Benzamido)phenyl)propionamido)-4-methyl-5-α-4-azaandrostan-3-one.

98) 17-Formamido-4-methyl-5-α-4-azaandrostan-3-one.

99) 17-(2-(Carbomethoxy)-1-cyclopentenylcarboxamido)-4-methyl-5-α-4-azaandrostan-3-one.

100) 17-(2,6-Difluorobenzamido)-4-methyl-5-α-4-azaandrostan-3-one.

101) 17-(2,3-Difluorobenzamido)-4,7-dimethyl-5-α-4-azaandrostan-3-one.

Table 2 illustrates the NMR data of some of the above examples.

TABLE 2
NMR DATA (PPM)

Example	Angular Methyls	Miscellaneous
10	0.68, 0.88	1.20 (-NHCOC(CH_3)$_3$)
11	0.72 0.88	1.17 (-NHCOC(CH_3)3)
12	0.67, 0.89	3.66 (-CO_2CH_3)
13	0.61, 0.88	2.93 (-4-NCH_3)
14	0.67, 0.89	1.24 (-SCH(CH_3)$_2$) 1.28
15	0.67, 0.88	1.18 (-NHCOC(CH_3)$_3$)
16	0.70, 0.88	1.98 (-NHCOCH_3)
17	0.72, 0.89	2.93 (-4-NCH_3)
18	0.57, 0.85	2.91 (-4-NCH_3) (split)
19	0.66, 0.88	2.92 (-4-NCH_3)
20	0.64, 0.88	2.24 (-$COCH_3$)
21	0.66, 0.88	2.93 (-4-NCH_3)
22	0.61, 0.87	3.78 (-$COCH_2$-(C_4H_3S))
23	0.70, 0.89	1.33 (-SC(CH_3)$_3$)
24	0.64, 0.88	5.12 (-CO_2CH_2Ph)
25	0.60, 0.88	3.52(d) (-Ph-(OCH_3)$_2$)
26	0.70, 0.89	3.66 (-CO_2CH_3)
27	0.70, 0.89	1.24 (-SCH(CH_3)$_2$) 1.28

TABLE 2 (CONTD)
NMR DATA (PPM)

Example	Angular Methyls	Miscellaneous
28	0.57, 0.87	2.91 (-4-NCH_3)
29	0.67, 0.88	2.92 (-4-NCH_3)
30	0.66, 0.88	2.92 (-4-NCH_3)
31	0.61, 0.86	2.92 (-4-NCH_3)
32	0.68, 0.88	(split) 1.24 (-$SCH(CH_3)_2$) 1.28
33	0.67, 0.89	2.93 (-4-NCH_3)
34	0.65, 0.88	4.56 (-OCH_2Ph)
35	0.68, 0.89	3.75 (-CO_2CH_3)
36	0.60, 0.86	4.92 (-$COCH(Ph)_2$)

Also included with the scope of this invention are 4-N-X analogs where X is OH, NH_2 or SCH_3. The 4-N-OH and 4-N-NH_2 derivatives can be made by incorporating hydroxylamine or hydrazine, respectively, in place of methylamine in the seco acid ring A closure for the starting androstanes herein as described in J. Med Chem. 29, 2298-2315 (1986) by Rasmusson et al. Further, reaction of the anion of the saturated 4-N-H androstanes, wherein the anion is generated from the 4-NH precursor by sodium hydride and methylsulfenyl chloride can produce the corresponding 4-N-5-CH_3 derivative. Thus, substituent R on the 4-N position also includes OH, NH_2 and S-CH_3.

The above examples are non-limiting and suitable acylating agents may readily be substituted according to the methods described in the present invention and reacted with a described amine to form the claimed amides. The following definitions further clarify the present invention.

The Rf values cited were carried out on standard thin layer chromatographic Si gel plates. The elution solvent system used is given in the parentheses following the Rf value.

The mass spectral values are given either as FAB, i.e., fast atom bombardment, or electron impact (EI) and are reported as molecular ion peaks, being (M), (M+1) or (M+2), the molecular weight, MW, or the MW plus one or two atomic units.

The nuclear magnetic resonance data was taken at 200 or 400 MHz in $CDCl_3$ and is tabulated for unique proton values of each compound at the end of the Examples. The coupling constant J is given in Hertz, Hz.

The invention further relates to all stereoisomers, diastereomers or enantiomers of the compounds depicted.

The term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds of this invention which are generally prepared by the free base with a suitable organic or inorganic acid. Representative salts include the following salts: Acetate, adipate, alginate, aspartate benzenesulfonate, benzoate, bicarbonate, bisulfate borate, butyrate, camsylate, carbonate, camphorate, chloride, citrate, digluconate, fumarate, glucoheptanate, gluconate, glutamate, glycerophosphate, hydrobromide, hydrochloride, hydroiodide, lactate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate.

The term "pharmaceutically effective amount" shall mean that amount or quantity of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that is being sought by a researcher or clinician or physician.

The term "aryl" shall mean a mono- or polycyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is defined to include H, C_{1-6}alkyl, arylC_{1-20}alkyl wherein the alkyl groups are unsubstituted or substituted with C_{1-8} alkyloxy, carboxyC_{0-10}alkyl, hydroxy, or halogen. The term "aryl" also encompasses those aromatic systems which independently have hydroxyl, C_{1-10}alkyl, C_{2-20}alkenyl, C_{1-20}alkyloxy, haloC_{1-}

$_{20}$alkyl, benzoyl, cyano, nitro, carboxamide, acetamido and halogens directly bonded to the aromatic carbon atom(s) or as further defined in the specification. The term aryl clearly includes unsubstituted or substituted with R as defined above phenyl, napthyl, anthracenyl of C_{6-14} carbon atoms and/or biphenyl.

The term "heteroaryl" shall mean a mono- or polycyclic system composed of 5- and 6-membered aromatic rings containing 1,2,3 or four heteroatoms chosen from N,O, or S and either unsubstituted or substituted with R as defined above independently or with hydroxyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20} alkenyl, haloC_{1-20}alkyl, benzoyl, cyano, nitro, carboamide, acetamide and halogens directly bonded to the aromatic carbon atom(s). The term heteroaryl is further defined to include heterocyclic species such as 5-7-membered monocyclic rings which are either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring so that a portion of the molecule is aromatic. Examples of heterocyclic species or elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrinidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiszolidinyl, indolyl, quinolinyl, isoquinolinyl, iminodibenzyl, benzimidazolyl, thiadiazolyl, thienyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Preferred embodiments clearly include those heteroaryl and heterocyclic species depicted in the specific examples.

The term "alkyl" shall mean straight or branched chain alkane.

The term "alkenyl" shall mean straight or branched chain alkene.

The term "alkynyl" shall mean straight or branched chain alkyne.

The term "cycloalkyl" shall mean cycloalkyl groups of C3-20 carbon atoms unsubstituted or substituted with typical cycloalkyl substituents such as those shown in the specific examples herein.

The term "cycloalkenyl" shall mean cycloalkenyl groups of C3-20 carbon atoms having one or more double bonds unsubstituted or substituted with typical cylcoalkenyl substituents such as those shown in the specific examples herein.

The term "arylalkyl" shall be taken to include an aryl portion as defined above and an alkyl portion as defined above.

The term "heteroarylalkyl" shall mean an heteroaryl portion as defined above and an alkyl portion as defined above.

The "C_{1-n}" designation where n may be an integer from 1 to 20 or 3-20 respectively refers to the alkyl portion, the cycloalkyl portion or to the alkyl portion of an arylalkyl or heteroarylalkyl unit. In addition, it refers to alkenyl, aryl or alkynl substituents.

The term "halogen" shall include fluorine, chlorine, iodine and bromine.

The term "oxy" shall mean an oxygen (O) atom.

The term "thio" shall mean a sulfur atom.

In the schemes and examples described in this disclosure, various reagent symbols have the following meanings:

PtO_2 is platinum oxide

TLC is thin layer chromatography

Na_2SO_4 is sodium sulfate

DMAP is 4-(dimethylamino)pyridine

DCC is N,N'-dicyclohexylcarbodiimide

The present invention has the objective of providing suitable topical, oral and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention.

The compositions containing the compounds of the present invention as the active ingredient for use in the treatment of e.g., benign prostatic hypertrophy, prostatitis, and treatment and prevention of prostatic carcinoma, hyperandrogenic conditions, can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration, as, for example, by oral administration in the form of tablets, capsules, solutions, or suspensions, or by injection. The daily dosage of the products may be varied over a wide range varying from 0.5 to 1,000 mg per adult human/per day. The compositions are preferably provided in the form of scored tablets containing 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.002 mg. to about 50 mg./kg. of body weight per day. Preferably the range is from about 0.01 mg. to 7 mg./kgs. of body weight per day. These dosages are well below the toxic dose of the product. For the treatment of androgenic alopecia, acne vulgaris, seborrhea, female hirsutism, the compounds of the present invention are administered in a pharmaceutical composition comprising the active compound in combination with a pharmacologically acceptable carrier adapted for topical, oral or parenteral administration.

These topical pharmaceutical compositions may be in the form of a cream, ointment, gel or aerosol formulation adapted for application to the skin. These topical pharmaceutical compositions containing the compounds of the present invention ordinarily include about 0.1% to 15%, preferably about 5%, of the active compound, in admixture with about 95% of vehicle.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills,

powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as a 5 α–reductase agent.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

Oral dosages of the present invention, when used for the indicated effects, will range between about Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as

"carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, zanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropyl- methacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid,

polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

BIOLOGICAL ASSAYS

Preparation of Human prostatic and scalp 5a-reductases.

Samples of human tissue were pulverized using a freezer mill and homogenized in 40 mM potassium phosphate, pH 6.5, 5 mM magnesium sulfate, 25 mM potassium chloride, 1 mM phenylmethylsulfonyl fluoride, 1 mM dithiothreitol (DTT) containing 0.25 M sucrose using a Potter-Elvehjem homogenizer. A crude nuclear pellet was prepared by centrifugation of the homogenate at 1,500xg for 15 min. The crude nuclear pellet was washed two times and resuspended in two volumes of buffer. Glycerol was added to the resuspended pellet to a final concentration of 20%. The enzyme suspension was frozen in aliquots at -80°C. The prostatic and scalp reductases were stable for at least 4 months when stored under these conditions.

5α-reductase assay.

The reaction mixture contained in a final volume of 100 µl is: 40 mM buffer (human scalp, potassium phosphate, pH 6.5; human prostatic 5α-reductase, sodium citrate, pH 5.5), 0.3-10 µM ^{14}C-T (or ^{3}H-T), 1 mM DTT, and 500 µM NADPH. Typically, the assay was initiated by the addition of 50-100 µg prostatic homogenate or 75-200 µg scalp homogenate and incubated at 37°C. After 10-50 min the reaction was quenched by extraction with 250 µl of a mixture of 70% cyclohexane: 30% ethyl acetate containing 10 µg each DHT and T. The aqueous and organic layers were separated by centrifugation at 14,000 rpm in an Eppendorf microfuge. The organic layer was subjected to normal phase HPLC (10 cm Whatman partisil 5 silica column equilibrated in 1 ml/min 70 % cyclohexane: 30 % ethyl acetate; retention times DHT, 6.8-7.2 min; androstanediol, 7.6-8.0; T, 9.1-9.7 min). The HPLC system consisted of a Waters Model 680 Gradient System equipped with a Hitachi Model 655A autosampler, Applied Biosystems Model 757 variable UV detector, and a Radiomatic Model A120 radio-

activity analyzer. The conversion of T to DHT was monitored using the radioactivity flow detector by mixing the HPLC effluent with one volume of Flo Scint I (Radiomatic). Under the conditions described, the production of DHT was linear for at least 25 min. The only steroids observed with the human prostate and scalp preparations were T, DHT and androstanediol.

Stumptail macaque protocol

The following protocol is utilized with the stumptail macaque monkey to demonstrate the effect of compounds of the present invention for promoting hair growth.

Twenty-one male stumptail macaque monkeys of species *Macaca speciosa* are assigned to vehicle control and drug treatment groups on the basis of baseline hair weight data. This assignment procedure is necessary to insure that the average baseline hair growth for each control and experimental group is comparable. The control and drug treatment groups are as follows:

1. Topical 50:30:20 vehicle (N = 6)
2. Oral 5α-reductase and topical 50:30:20 vehicle (N = 5)
3. Oral placebo (N = 5)
4. 5α-reductase in vehicle (N = 5)

The vehicle consists of 50% propylene glycol, 30% ethanol and 20% water. A 100 mM concentration of topical 5α-reductase is formulated in this vehicle. The same 5α-reductase is administered as an oral dose of 0.5mg per monkey. Immediately prior to the dosing phase of the study, hair is removed from a 1 inch square area (identified by four tatoos) in the center of the balding scalp. This hair collection is the baseline hair growth determination prior to the beginning of treatment. Approximatly 250μL of vehicle and 5α-reductase in vehicle is prepared and topically administered to the tatooed area of the scelp. The selected 5α-reductase and placebo is ingested by the monekys at the same time as

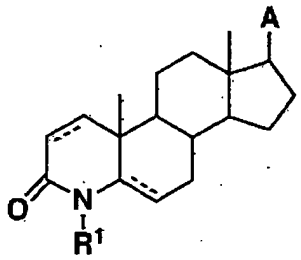
the topical doses are administered. The monkeys are dosed once per day, seven days per week for twenty weeks.

At four week intervals throughout the dosing phase of the study, each monkey is shaved and the hair is collected and weighed. The body weight data (at baseline and during assay) is analyzed by the nonparametric Wilcoxon rank-sum test. Differences are significant at $p < 0.05$. Hair weight data at each week collection for vehicle, placebo and treatment groups are expressed as the change from baseline. Statistical analysis is performed on the rank of the data to show overall differences among groups at each four week collection.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula:



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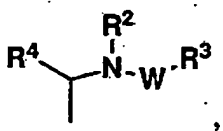
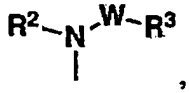
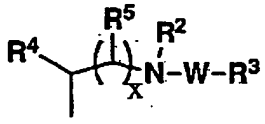
and the pharmaceutically acceptable salts thereof, wherein:

A is:

(a)  ,

(b)  , except when R^2 equals H, there is a 5αH and W equals C(O), R^3 can not be C_{1-12} alkyl,

(c)  ; wherein

R^1 is:

H,
methyl or ethyl;

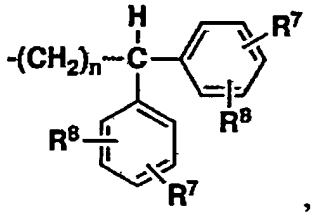
R^2 is:

H, or
C_{1-20} alkyl;

R^3 is:

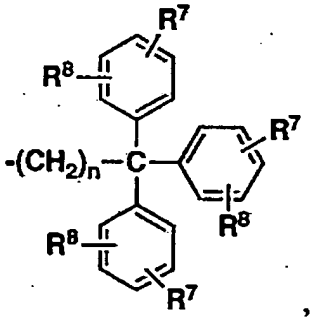
H,
aminoC_1-C4alkyl,
mono C_1-C4alkylaminoC_1-C4alkyl,
di C_1-C4alkylaminoC_1-C4alkyl,
mono C_1-C4 alkylaminoaryl,
di C_1-C4 alkylaminoaryl,
C_{1-20} alkyl,
C_{6-14} aryl,
heteroaryl,
C_{6-14} arylC_{1-20}alkyl,
heteroarylC_{1-20}alkyl,
C_{1-20}alkylthioC_{1-20}alkyl,
C_{1-20}alkylsulfinylC_{1-20}alkyl,
C_{1-20}alkylsulfonylC_{1-20}alkyl,
C_{0-10}alkylC_{6-14}arylthioC_{1-20}alkyl,
C_{0-10}alkylC_{6-14}arylsulfinylC_{1-20}alkyl,
C_{0-10}alkylC_{6-14}arylsulfonylC_{1-20}alkyl,
C_{1-20}alkyloxycarbonylC_{1-20}alkyl,
carboxylC_{1-20}alkyl,
carboC_{1-20}alkyloxyC_{1-20}alkyl,
C_{1-20}alkylcarbonylC_{1-20}alkyl,
carboxylC_{1-20}alkyl,
C_{1-20}alkylcarbonylC_{1-20}alkyl,
C_{3-20}cycloalkyl,
C_{3-20}cycloalkenyl,
C_{3-20}cycloalkylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,

haloC1-20alkyl,
hydroxylC1-20alkyl,
iminodibenzylC1-20alkylC6-14aryl,
halohydroxylC1-20alkyl,
thiosulfatoC1-20alkyl,
C6-14 arylC1-20alkyloxyC1-20alkyl,
C1-20alkyloxyC1-20alkyl,
C6-14 arylcarbonylC6-14arylC1-20alkyl,
diarylC1-20alkyl of the formula:



, n equals 0-19;

triarylC1-20alkyl of the formula:



, n equals 1-19;

C2-20 alkenyl,
C2-20 alkenylC1-20alkyl,
C6-14aryloxyC6-14aryl,
heteroarylC2-20alkenyl,
C6-14 arylC2-20alkenyl,
C2-20alkynylC1-20alkyl,
C6-14arylcarboamideC6-14arylC1-20alkyl,
phosphonoC1-20alkyl,
C6-14 arylC2-20alkynylC1-20alkyl, or

heteroarylC2-20alkynylC1-20alkyl;

R^4 is:

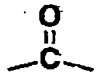
H,
C_{1-20} alkyl,
C_6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC1-20alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC1-20alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen; or
heteroaryl;

R^5 can be the same or different when x is greater than 1 and is:
H, or
C_{1-12} alkyl;
R^7 or R^8 are:

H,
CH_3,
C_2H_5,
carboxamido,
C_{1-6} alkylthio,
C_1-C_6 alkylsulfinyl,
C_1-C_6 alkylsulfonyl,
OCH_3,
NH_2,
CH_3NH,
$(CH_3)_2N$,
OH,

NO_2,
CN,
F,
acetamido,
Cl,
OC_2H_5,
CF_3,
isopropyl, or
isobutyl; n equals 1-10 and the C_{1-20} alkyl portion is optionally substituted with R^5;

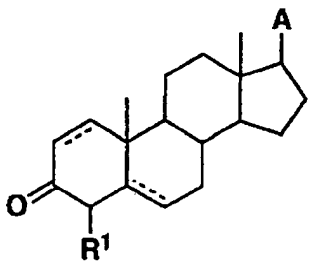
W is:

 , or

 ;

x is an integer from 1-25;
and the dashes indicate a double bond is optionally present.

2. A compound according to Claim 1 of the formula:



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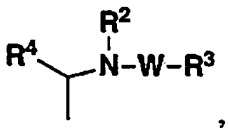
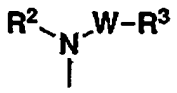
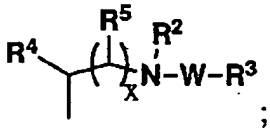
and the pharmaceutically acceptable salts thereof, wherein:

A is:

(a)  ,

(b)  except when R^2 equals H, there is a 5alphaH and W equals C(O), R^3 can not be C_{1-12} alkyl,

(c)  ; wherein

R^1 is:

H,
methyl, or ethyl;

R^2 is:

H, or
C_{1-20}alkyl;

R^3 is:

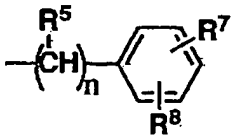
H,

C_{1-20}alkyl is a straight or branched chain alkane of up to 20 carbon atoms;

C_{6-14} aryl wherein aryl is a mono or polycyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen;

heteroaryl which is a mono or polycyclic system composed of 5- or 6-membered aromatic rings consisting of 1,2, 3 or 4 heteroatoms chosen from N, O, or S and either unsubstituted or substituted with R or independently with hydroxyl, C_{1-20}alkyloxy, C_{1-20}alkyl, benzoyl, carboamide, acetamide, halogens, C_{2-20}alkenyl, cyano, nitro, or haloalkyl directly bonded to the aromatic carbon atoms(s);

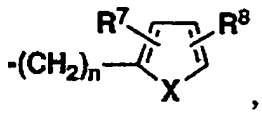
C_{6-14} arylC_{1-20}alkyl of the formula:



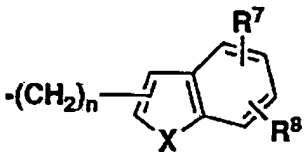
wherein the aromatic ring is optionally and independently substituted with R^7 and R^8 wherein R^7 and R^8 are H,

CH_3,
C_2H_5,
carboxamido,
C_1-C_6 alkylthio,
C_1-C_6 alkylsulfinyl,
C_1-C_6 alkylsulfonyl,
OCH_3,
NH_2,
CH_3NH,
$(CH_3)_2N$,
OH,
NO_2,
CN,
F,
acetamido,
Cl,
OC_2H_5,
CF_3,
isopropyl, or
isobutyl; n equals 1-10 and the C_{1-20}alkyl portion is optionally substituted with R^5;

HeteroarylC$_{1-20}$alkyl of the formula:



, or



wherein X equals O, S, or NR; and n equals 1-10;

C$_{1-20}$alkylsulfonylC$_{1-20}$alkyl.

C_{1-20}alkylthioC_{1-20}alkyl,
C_{1-20}alkylsulfinylC_{1-20}alkyl of the formula:

$-(CH_2)_nS(O)_p-R^9$ wherein R^9 is
C_{0-10}alkylC_{6-14}aryl,
CH_3,
C_2H_5,
C_3H_7,
C_4H_9,
isopropyl,
isobutyl,
sec-butyl,
t-butyl,
isopentyl,
neopentyl, or
ixohexyl; n equals 1-15 and p=0-2;

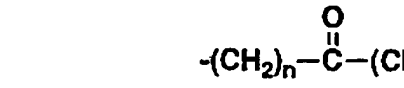
C_{1-20}alkyloxycarbonylC_{1-20}alkyl of the formula:

$-(CH_2)_n-\overset{O}{\overset{\|}{C}}-OR^{10}$ wherein R^{10} is:
CH_3,
C_2H_5,
C_3H_7,
C_4H_9, or
C_5H_{11}; and n equals 1-20;

CarboxylC_{1-20}alkyl of the formula:

$-(CH_2)_n-\overset{O}{\overset{\|}{C}}-OH$; n = 1-20;

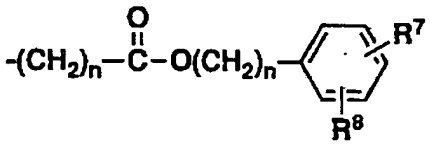
C_{1-20}alkylcarbonylC_{1-20}alkyl of the formula



, n equals 1-20;
m equals 0-19;

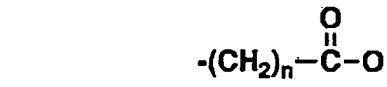
C_{3-20}cycloalkylC_{1-20}alkyl of the formula:
$-(CH_2)_n$-(cycloalkyl) wherein the cycloalkyl protion is a monocyclic, bicyclic, or polycyclic hydrocarbon of up to 20 carbon atoms wherein the rings are optionally substituted with R^1; and n = 1-20;

ArylC_{1-20}alkyloxycarbonylC_{1-20}alkyl of the formula:



wherein n = 1-20;

HeteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl of the formula:

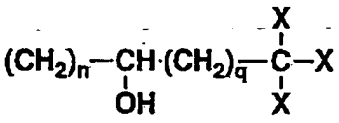


wherein Heteroaryl is as defined and n = 1-20;

haloC_{1-20}alkyl of the formula:
$-(CH_2)_n-CH_2X$ wherein
X equals Br, Cl, F or I; n is 1-19;

hydroxylC_{1-20}alkyl of the formula:
$-(CH_2)_nCH_2OH$; n is 1-19;

halohydroxylC_{1-20}alkyl of the formula:



wherein

n = 1-18

q = 0-18

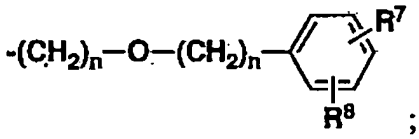
n + q = 0-18 and

X equals Br, Cl, F or I;

ThiosulfatoC1-20alkyl of the formula:
-(CH2)nCH2SSO3Na; n is 1-19;

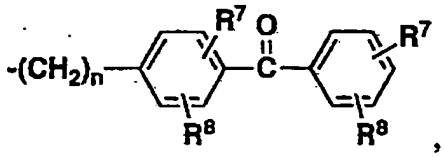
phosphonoC1-20alkyl of the formula:
-(CH2)nP(O)(OR)2 wherein R is lower alkyl and n is 1-20;

ArylC1-20alkyloxyC1-20alkyl of the formula:



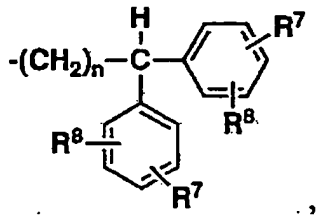
; n is 1-20;

ArylcarbonylarylC1-20alkyl of the formula:



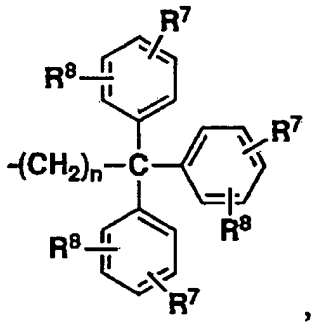
, n equals 1-20;

DiarylC1-20alkyl of the formula:



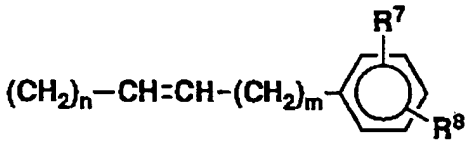
, n equals 0-19;

TriarylC1-20alkyl of the formula:



, n equals 1-19;

Aryl C2-20alkenyl of the formula:



n = 0-18
m = 0-18
m+n = 0-18;

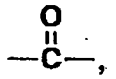
R^4 is

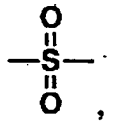
H,
C1-20alkyl,
C6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C1-6 alkyl, arylC1-20alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C1-8alkyloxy, carboxy C0-10alkyl, or halogen or aryl directly substituted independently with amino, mono C1-C4 alkylamino, di C1-C4 alkylamino, mono C1-C4 alkylaminoaryl, di C1-C4 alkylaminoaryl, hydroxyl, haloC1-20alkyl, carboxamido, benzoyl, C1-20alkyloxy, C1-20alkyl, C2-20alkenyl, cyano, nitro, acetamide or halogen; or

heteroaryl;

R^5 can be the same or different when x is greater than one and is;
H, or
C_{1-12}alkyl;

W is:

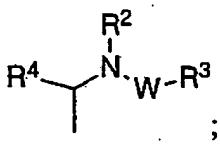
 , or

 ,

x is an integer from 1-10;

and the dashes indicate a double bond is optionally present.

3. A compound according to Claim 1 and the pharmaceutically acceptable salts thereof, wherein,

A is:  ;

R^1 is:

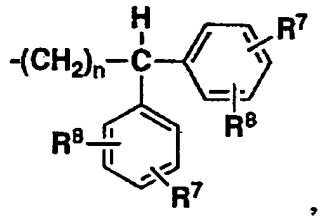
H,
methyl or ethyl;

R^2 is:

H, or
C_{1-12} alkyl;

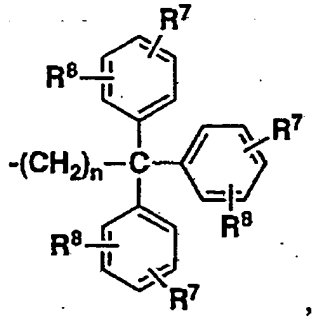
R^3 is:

H,
C_{1-20} alkyl,
C_{6-14} aryl,
heteroaryl,
C_{6-14} arylC_{1-20}alkyl,
heteroarylC_{1-20}alkyl,
C_{1-20}alkylthioC_{1-20}alkyl,
C_{1-20}alkyloxycarbonylC_{1-20}alkyl,
carboxylC_{1-20}alkyl,
C_{1-20} alkylcarbonylC_{1-20}alkyl,
C_{3-20}cycloalkyl,
C_{3-20}cycloalkylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
haloC_{1-20}alkyl,
hydroxyC_{1-20}alkyl,
halohydroxyC_{1-20}alkyl,
thiosulfatoC_{1-20}alkyl,
C_{6-14} arylcarbonylC_{6-14}arylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxyC_{1-20}alkyl,
C_{1-20}cycloalkylC_{1-20}alkyl,
diarylC_{1-20}alkyl of the formula:



, n equals 0-19;

triarylC_{1-20}alkyl of the formula:



, n equals 1-19; or

C_{2-20} alkenyl;

R^4 is:

H,
C_{1-20} alkyl,
C_{6-14} aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen; or
heteroaryl.

4. A compound according to Claim 3 and the pharmaceutically acceptable salts thereof wherein:

R^1 is:
H,
methyl, or
ethyl;

R^2 is:

H,
methyl,
ethyl, linear or branched:
propyl,
butyl,
pentyl,
hexyl, or heptyl;

R^3 is:

t-butyl,
2,2-diphenylethyl,
3-thienyl,
2-thienyl,
11-(isopropylthio)undecyl,
7-(carbomethoxy)heptyl,
1-(1-(4-isobutylphenyl-)ethyl,
7-(carboxy)heptyl,
acetylmethyl,
1-adamantylmethyl,
2-thienylmethyl,
2-(carbobenzyloxy)ethyl,
3,4-dimethoxyphenyl,
phenyl,
5-bromopentyl,
phenylthiomethyl,
t-butylthiomethyl,
3-methyl-2-thienyl,
5-methyl-2-thienyl,
11-hydroxyundecyl,
1-(4-nitrophenyl)ethyl,

isopropylthiomethyl,
5-(thiosulfato)pentyl,
benzyloxymethyl,
carbomethoxymethyl,
diphenylmethyl,
triphenylmethyl,
2-furyl,
4-isopropylphenyl,
cyclohexylmethyl,
4-methylcyclohexyl,
3-(3-indolyl)propyl,
3-Indolylmethyl,
4-isobutylphenyl,
4-nitrophenyl,
3-nitrophenyl,
3-acetamidomethyl,
4-ethoxyphenyl,
hexadecyl,
stearyl,
3,5-Bis(trifluoromethyl)benzyl,
3-cyanophenyl,
heptafluoropropyl,
4-benzoylphenyl,
5-benztriazolyl,
3,5-difourophenyl,
bis(4-isopropylphenyl)methyl,
2-hydroxyphenyl,
phenylvinyl,
2-hydroxy-3,3,3-trichloropropyl,
methyl,
allyl,
n-propyl,
n-octyl,
isopropyl,

(isopropylthio)methyl,
isobutyl,
ethyl,
2,2,2-triphenylethyl,
benzyl,
octadecyl,
2(ethyl)phenyl,
3(chloro)phenyl,
4(methyl)phenyl,
2,3(dichloro)phenyl,
2,6(dichloro)phenyl,
4(fluoro)phenyl,
3(methoxy)phenyl,
3-(acetamido)phenyl,
3-(Iminodibenz-5-ylmethyl)phenyl,
3-trifluoromethylphenyl,
2(ethoxy)phenyl,
formyl,
2-napthyl, or
2-thiazolyl;

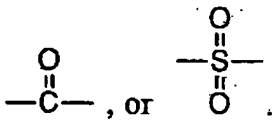
R^4 is:

H,
methyl,
ethyl, linear or branched:
propyl,
butyl,
C_{6-14} aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with

amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_1-$_{20}$alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen; or

heteroaryl;

W is:



5. The compound according to Claim 4 and the pharmaceutically acceptable salts thereof, wherein the compound is selected from:

4-Methyl-20(trimethylacetamido)5α-4-aza-pregnan-3-one,

4-Methyl-17β(trimethylacetamidomethyl)-4-aza-5α-androstan-3-one,

4-Methyl-17β(2-thiophenesulfonamidomethyl)-4-aza-5α-androstan-3-one,

17β(Isopropylthiododecanoylamidomethyl)-4-aza-5α-androstan-3-one,

4-Methyl-17β(thiophenecarboxamidomethyl)-4-aza-5α-androstan-3-one,

17β(Carbomethoxyoctanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(2-(4-isobutylphenyl)propionamidomethyl)-4-Methyl-4-aza-5α-androstan-3-one,

17β(8-Carboxyoctanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(Acetoacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

4-Methyl-17β(2-thiopheneacetamidomethyl)-4-aza-5α-androstan-3-one,

17β(3-(carbobenzyloxy)propioamidomethyl)-4-Methyl-4-aza-5α-androstan-3-one,

17β(3,4-dimethoxyphenylacetamidomethyl)-4-Methyl-4-aza-5α-androst-3-one,

17β(Benzenesulfonamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(6-Bromohexanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(12-Hydroxydodecanoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

4-Methyl-17β(2-(4-nitrophenyl)propionamidomethyl)-4-aza-5α-androstan-3-one,

17β(Isopropylthioacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

4-Methyl-17β(6-(thiosulfato)hexanoylamidomethyl)-4-aza-5α-androstan-3-one,

17β(Benzyloxyacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(Carbomethoxyacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(Diphenylacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

4-Methyl-17β(3,3,3-triphenylpropionamidomethyl)-4-aza-5α-androstan-3-one,

17β(2-Furylacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(4-Isopropylphenylacteamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(Cyclohexylacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(3-indolylacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

4-Methyl-17β(4-Methylcyclohexanecarboxamidomethyl)-4-aza5α-androstan-3-one,

17β(4-(3-Indolyl)-butyramidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(4-Isobutylbenazmidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(Acetoxyacetamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(6-Bromohexanoylamidomethyl)-4-Methyl-4-aza-5α-androstan-3-one,

20-((3-Acetamido)benzamido)-4-Methyl-4-aza-5α-pregnan-3-one,

17β(4-Ethoxybenzamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(Iminodibenzyl-5-carboxamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

4-Methyl-20-(stearoylamido)-4-aza-5α-pregnan-3-one,

4-Methyl-17β-(3,5-bis-(trifluoromethyl)benzamidomethyl)-4-aza-5α-androstan-3-one,

17β(3-Cyanobenzamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β(Benztriazole-5-carboxamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

20-(3,5-diflurobenzamido)-4-methyl-4-aza-5α-pregnan-3-one,

17β(Bis-(4-Isopropyl)phenyl)acetamidomethyl-4-methyl-aza-5α-androstan-3-one,

17β(Cinnamoylamidomethyl)-4-methyl-4-aza-5α-androstan-3-one,

17β((3-Hydroxy-4,4,4-trichlorobutyramido)methyl)-4-methyl-4-aza-5α-androstan-3-one,

17-(2,6-Dichlorobenzamidomethyl)-5-α-4-methyl-4-azaandrosatan-3-one,

17-(3-Nitrobenzoylamidomethyl)-5-α-4-methyl-4-azaandrostan-3-one,

17-(4-Nitrobenzoylamidomethyl)-5-α-4-methyl-4-azaandrostan-3-one,

17-(3,3-Diphenylpropionamidomethyl)-5-α-4-methyl-4-azaandrostan-3-one,

17-((3-(Iminodibenz-5-ylmethyl)benzoyl)aminomethyl)-4-methyl-5-α-4-azaandrostan-3-one,

17-(3-Hydroxy-4,4,4,-trichlorobutyroylamidomethyl))-5-α-4-methyl-4-azaandrostan-3-one,

17-Formamidomethyl-5-α-4-methyl-4-azaandrostan-3-one,

4-Methyl-17-(3,3,3,-triphenylpropionamidomethyl)-5-α-4-azaandrostan-3-one,

20-((Isopropylthio)acetamido)-4-methyl-5-α-4-azapregnan-3-one,

20-((Isopropylthio)acetamido)-5-α-4-azapregnan-3-one,

4-Methyl-17-((phenylthio)acetamidomethyl)-5-α-4-azaandrostan-3-one,

17-((t-Butylthio)acetamidomethyl)-5-α-4-methyl-4-azaandrostan-3-one,

17-(3-Methyl-2-thenoylaminomethyl)-4-methyl-5-α-4-azaandrostan-3-one,

17-(5-Methyl-2-thenoylaminomethyl)-4-methyl-5-α-4-azaandrostan-3-one,

4-Methyl-17-(3-(trifluoromethyl)-benzamidomethyl)-5-α-4-azaandrostan-3-one, or

17-Benzamidomethyl-4-methyl-5-α-4-azaandrostan-3-one.

6. The compound according to Claim 4 and the pharmaceutically acceptable salts thereof, wherein the compound is selected from:

4-Methyl-20(trimethylacetamido)5α-4-aza-pregn-1-en-3-one,

4-Methyl-17ß(trimethylacetamidomethyl)-4-aza-5α-androst-1-en-3-one,

4-Methyl-17ß(2-thiophenesulfonamidomethyl)-4-aza-5α-androst-1-en-3-one,

17ß(isopropylthiododecanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

4-Methyl-17ß(thiophenecarboxamidomethyl)-4-aza-5α-androst-1-en-3-one,

17ß(-8-(Carbomethoxy)octanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(2-(4-Isobutylphenyl)propionamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(8-Carboxyoctanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(Acetoacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(1-Adamantylacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

4-Methyl-17ß(2-thiopheneacetamidomethyl)-4-aza-5α-androst-1-en-3-one,

17ß(3-(Carbobenzyloxy)propionamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(3,4-Dimethoxyphenylacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(Benzenesulfonamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(6-Bromohexanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(12-Hydroxydodecanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

4-Methyl-17ß(2-(4-nitrophenyl)propionamidomethyl)-4-aza-5α-androst-1-en-3-one,

17ß(Isopropylthioacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

4-Methyl-17ß(6-(thiosulfato)hexanoylamidomethyl)-4-aza-5α-androst-1-en-3-one,

17ß(Benzyloxyacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(Carbomethoxyacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(Diphenylacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

4-Methyl-17ß(3,3,3-triphenylpropionamidomethyl)-4-aza-5α-androst-1-en-3-one,

17ß(2-Furylacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(4-Isopropylphenylacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(Cyclohexylacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(3-Indolylacetamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

4-Methyl-17ß(4-methylcyclohexanecarboxamidomethyl)-4-aza-5α-androst-1-en-3-one,

17ß(4-(3-Indolyl)-butyramidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(4-Isobutylbenzamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß(Acetoxyacetamidomethyl)-4-methyl-4-aza-5α-

androst-1-en-3-one,

17ß(6-Bromohexanoylamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

20-((3-Acetamido)benzamido)-4-methyl-4-aza-5α-pregn-1-en-3-one,

17ß(4-Ethoxybenzamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß-(Iminodibenzyl-5-carboxamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

4-Methyl-20-(stearoylamido)-4-aza-5α-pregn-1-en-3-one,

4-Methyl-17ß-(3,5-Bis-(trifluoromethyl)benzamido-methyl)-4-aza-5α-androst-1-en-3-one,

17ß-(3-Cyanobenzamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17ß-(Benztriazol-5-carboxamidomethyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

20-(3,5-Difluorobenzamido)-4-methyl-4-aza-5α-pregn-1-en-3-one,

17ß-(Bis-(4-Isopropyl)phenyl)acetamidomethyl-4-methyl-aza-5α-androst-1-en-one,

17ß-(Cinnamoylamidomethyl)-4-Methyl-4-aza-5α-androst-1-en-3-one,

17ß-((3-Hydroxy-4,4,4,-trichlorobutyramido)methyl)-4-methyl-4-aza-5α-androst-1-en-3-one,

17-(2,6-Dichlorobenzamidomethyl)-5-α-4-methyl-4-azaandrosatan-1-en-3-one,

17-(3-Nitrobenzoylamidomethyl)-5-α-4-methyl-4-azaandrostan-1-en-3-one,

17-(4-Nitrobenzoylamidomethyl)-5-α-4-methyl-4-azaandrostan-1-en-3-one,

17-(3,3-Diphenylpropionamidomethyl)-5-α-4-methyl-4-azaandrostan-1-en-3-one,

17-((3-(Iminodibenz-5-ylmethyl)benzoyl)aminomethyl)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(3-Hydroxy-4,4,4,-trichlorobutyroylamidomethyl))-5-α-4-methyl-4-azaandrostan-1-en-3-one,

17-Formamidomethyl-5-α-4-methyl-4-azaandrostan-1-en-3-one,

4-Methyl-17-(3,3,3,-triphenylpropionamidomethyl)-5-α-4-azaandrostan-1-en-3-one,

20-((Isopropylthio)acetamido)-4-methyl-5-α-4-azapregnan-1-en-3-one,

20-((Isopropylthio)acetamido)-5-α-4-azapregnan-1-en-3-one,

4-Methyl-17-((phenylthio)acetamidomethyl)-5-α-4-azaandrostan-1-en-3-one,

17-((t-Butylthio)acetamidomethyl)-5-α-4-methyl-4-azaandrostan-1-en-3-one,

17-(3-Methyl-2-thenoylaminomethyl)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(5-Methyl-2-thenoylaminomethyl)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(3-(trifluoromethyl)-benzamidomethyl)-5-α-4-azaandrostan-1-en-3-one,

17-(2,6-Dichlorobenzamidomethyl)-5-α-4-methyl-4-azaandrosatan-1-en-3-one,

17-(3-Nitrobenzoylamidomethyl)-5-α-4-methyl-4-azaandrostan-1-en-3-one,

17-(4-Nitrobenzoylamidomethyl)-5-α-4-methyl-4-azaandrostan-1-en-3-one,

17-(3,3-Diphenylpropionamidomethyl)-5-α-4-methyl-4-azaandrostan-1-en-3-one,

17-((3-(Iminodibenz-5-ylmethyl)benzoyl)aminomethyl)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(3-Hydroxy-4,4,4,-trichlorobutyroylamidomethyl))-5-α-4-methyl-4-azaandrostan-1-en-3-one,

17-Formamidomethyl-5-α-4-methyl-4-azaandrostan-1-en-3-one,

4-Methyl-17-(3,3,3,-triphenylpropionamidomethyl)-5-α-4-azaandrostan1-en-3-one,

20-((Isopropylthio)acetamido)-4-methyl-5-α-4-azapregnan-1-en-3-one,

20-((Isopropylthio)acetamido)-5-α-4-azapregnan-1-en-3-one,

4-Methyl-17-((phenylthio)acetamidomethyl)-5-α-4-azaandrostan-1-en-3-one,

17-((t-Butylthio)acetamidomethyl)-5-α-4-methyl-4-azaandrostan-1-en-3-one,

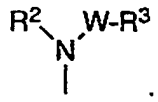
17-(3-Methyl-2-thenoylaminomethyl)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(5-Methyl-2-thenoylaminomethyl)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(3-(trifluoromethyl)-benzamidomethyl)-5-α-4-azaandrostan-1-en-3-one, or

17-Benzamidomethyl-4-methyl-5-α-4-azaandrostan-1-en-3-one.

7. A compound according to Claim 1 and the pharmaceutically acceptable salts thereof, wherein
A is:



; except when R^2 equals H, there is a 5αH and W equals C(O), R^3 can not be C_{1-12} alkyl

R^1 is:

H,
methyl or ethyl;

R^2 is:

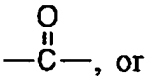
H, or
C_{1-12} alkyl;

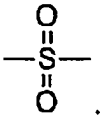
R^3 is:

H,
C_{1-20} alkyl,
C_{6-14} aryl,
heteroaryl,

aminoC$_1$-C$_4$alkyl,
mono-C$_1$-C$_4$alkylaminoC$_1$-C$_4$alkyl,
di C$_1$-C$_4$alkylaminoC$_1$-C$_4$alkyl,
C$_{5-14}$ arylC$_{1-20}$alkyl,
heteroarylC$_{1-20}$alkyl,
C$_{1-20}$alkylthioC$_{1-20}$alkyl,
C$_{1-20}$alkylsulfonylC$_{1-20}$alkyl,
C$_{1-20}$alkylsulfinylC$_{1-20}$alkyl,
C$_{1-20}$ alkyloxycarbonylC$_{1-20}$alkyl,
carboxyC$_{1-20}$alkyl,
carboC$_{1-20}$alkyloxyC$_{1-20}$alkyl,
C$_{1-20}$ alkylcarbonylC$_{1-20}$alkyl,
C$_{1-20}$cycloalkyl,
C$_{1-20}$cycloalkylC$_{1-20}$alkyl,
C$_{6-14}$ arylC$_{1-20}$alkyloxycarbonylC$_{1-20}$alkyl,
heteroarylC$_{1-20}$alkyloxycarbonylC$_{1-20}$alkyl,
haloC$_{1-20}$alkyl,
hydroxylC$_{1-20}$alkyl,
halohydroxyC$_{1-20}$alkyl,
thiosulfatoC$_{1-20}$alkyl,
C$_{6-14}$ arylC$_{1-20}$alkyloxyC$_{1-20}$alkyl,
C$_{6-14}$ arylcarbonylC$_{5-14}$arylC$_{1-20}$alkyl,
diarylC$_{1-20}$ alkyl,
triarylC$_{1-20}$alkyl,
C$_{2-20}$ alkenyl,
phosphonoC$_{1-20}$alkyl,
C$_{2-20}$ alkenylC$_{1-20}$alkyl,
heteroarylC$_{2-20}$alkenyl,
C$_{6-14}$ arylC$_{2-20}$alkenyl,
C$_{2-20}$alkynylC$_{1-20}$alkyl,
C$_{6-14}$ arylC$_{2-20}$alkynylC$_{1-20}$alkyl, or
heteroarylC$_{2-20}$alkynylC$_{1-20}$alkyl;

W is:

 , or

 .

8. A compound according to Claim 7 and the pharmaceutically acceptable salts thereof wherein:

R^1 is:

H,
methyl,
ethyl,

R^2 is:

H,
methyl,
ethyl, linear or branched:
propyl,
butyl,
pentyl,
hexyl, or
heptyl;

R^3 is:

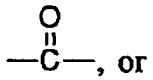
t-butyl,
3-thienyl,
2-thienyl,
4-pyrdinyl,
2-pyridinyl,
3-pyridinyl,
(2(3-benzamido)phenyl)ethyl,
t-rifluoromethyl,

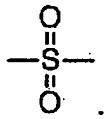
2,3-difluorophenyl,
2-methylphenyl,
2,3-dimethylphenyl,
cinnamoyl,
formyl,
2-propyl,
3-methylbutyl,
2-(carbomethoxy)-1-cyclopentenyl,
2,6-difluorophenyl,
2,3-difluorophenyl,
2,6-dichlorophenyl,
t-butylmethyl,
t-butylthiomethyl,
(phenyl)methyl,
phenylthiomethyl,
11-(isopropylthio)undecyl,
7-(carbomethoxy)heptyl,
3-carboxy-3-methylbutyl,
3-(carbomethoxy)-3-methylbutyl,
3-(carbomethoxy)-2,2-dimethylpropyl,
1-(1-(4-isobutylphenyl))ethyl,
7-(carboxy)heptyl,
acetoxymethyl,
1-methyl-2-pyrrole,
5-(diethylphosphono)pentyl,
2-(4'-fluoro-3,5,3'-trimethylbiphen-2-yl)ethyl,
2-phenylpropyl,
2,2-dimethylethylenyl,
4-benzyloxyphenyl,
2,4,4-trimethylpentyl,
benzylthiomethyl,
benzthiophen-3-yl,
2-hydroxy-2-propyl,
2-acetoxy-2-propyl,

1-adamantylmethyl,
2-thienylmethyl,
2-(phenyl)propyl,
2-(carbobenzyloxy)ethyl,
3,4-dimethoxyphenyl,
-phenyl,
5-bromopentyl,
11-hydroxyundecyl,
1-ethyl-4-nitrobenzene-1-yl,
isopropylthiomethyl,
5-(thiosulfato)pentyl,
benzyloxymethyl,
carbomethoxymethyl,
diphenylmethyl,
triphenylmethyl,
1-methyl-2-pyrrolyl,
3-carboxy-3-methylbutyl,
2-furyl,
5-(Diethylphosphono)pentyl,
4-isopropylphenyl,
cyclohexylmethyl,
4-methylcyclohexyl,
3-(3-Indolyl)propyl,
3-Indolylmethyl,
4-isobutylphenyl,
4-nitrophenyl,
3-nitrophenyl,
2,3-difluorophenyl,
3-fluoro-2-methylphenyl,
2-fluorophenyl,
2,2-dimethylethylenyl,
3-acetamidomethyl,
4-ethoxyphenyl,
3-(2-nitrophenoxy)propyl,

hexadecyl,
stearyl,
3,5-Bis(trifluoromethyl)phenyl,
3-cyanophenyl,
4-cyanophenyl,
2,4,4-trimethylpentyl,
t-butylmethyl,
benzyl,
heptafluoropropyl,
5-benztriazolyl,
3,5 difluorophenyl,
Bis(4-isopropylphenyl)methyl,
2-hydroxyphenyl,
2-phenylvinyl, or
2-hydroxy-3,3,3-trichloropropyl;

W is:

 , or



9. The compound according to Claim 8 and the pharmaceutically acceptable salts thereof, wherein the compound is selected from:

17ß(12-(t-Butylthio)dodecanoylamido)-4-methyl-4-aza-5α-androstan-3-one,

4-Methyl-17ß(8-(carbomethoxy)octanoylamido)-4-aza-5α-androstan-3-one,

17ß(Isopropylthiododecanoylamido)-4-methyl-4-aza-5α-

androstan-3-one,

4-Methyl-17ß(3-thienylamido)-4-aza-5α-androstan-3-one,

17-Benzoylamido-5-α-4-methyl-4-azaandrostan-3-one,

17-(2-Thiophenesulfonamido)-5-α-4-methyl-4-azaandrostan-3-one,

4-Methyl-17-(phenylthioacetamido)-5-α-4-methyl-4-azaandrostan-3-one,

4-Methyl-17-(4-methylpentanoylamido)-5-α-4-azaandrostan-3-one,

4-Methyl-17-(3-thenoylamino)-5-α-4-azaandrostan-3-one,

17-(3-(4'-Fluoro-3,5,3'-trimethylbiphen-2-yl)propionamido)-4-methyl-5-α-4-azaandrostan-3-one,

17-(6-(Diethylphosphono)hexanoylamino)-4-methyl-5-α-4-azaandrostan-3-one,

17-((t-Butylthio)acetamido)-4-methyl-5-α-4-azaandrostan-3-one,

4-Methyl-17-(3-thiophenacetamido)-5-α-4-azaandrostan-3-one,

4-Methyl-17-(4-nitrobenzamido)-5-α-4-azaandrostan-3-one,

4-Methyl-17-(3-nitrobenzamido)-5-α-4-azaandrostan-3-one,

17-(2-Fluorobenzamido)-4-methyl-5-α-4-azaandrostan-3-one,

17-(4-cyanobenzamido)-4-methyl-5-α-4-zazaandrostan-3-one,

17-(Benzthiophen-3-ylacetamido)-4-methyl-5-α-4-azaandrostan-3-one,

4-Methyl-17-(2-thiophenecarboxamido)-5-α-4-azaandrostan-3-one,

17-(1-Methyl-2-pyrrolecarboxamido)-4-methyl-5-α-4-azaandrostan-3-one,

17-(4-Carboxy-4methylpentanoylamido)-4-methyl-5-α-4-azaandrostan-3-one,

17-(4-Carbomethoxy-4-methylpentanoylamido)-4-methyl-5-α-4-azaandrostan-3-one,

17-(4-Carbomethoxy-3,3-dimethylbutyroylamido)-4-methyl-5-α-4-azaandrostan-3-one,

4-Methyl-17-(3-phenylbutyroylamido)-5-α-4-azaandrostan-3-one,

17-(2,3-Difluorobenzoylamido)-4-methyl-5-α-4-azaandrostan-3-one,

4-Methyl-17-(2-methylbenzoylamido)-5-α-4-azaandrostan-3-one,

17-(2,3-Dimethylbenzamido)-4-methyl-5-α-4-azaandrostan-3-one,

17-Cinnamoylamido-4-methyl-5-α-4-azaandrostan-3-one,

17-(3,3-Dimethylacrylamido)-4-methyl-5-α-4-azaandrostan-3-one,

17-(3,4-Dimethoxybenzamido)-4-methyl-5-α-4-azaandrostan-3-one,

17-(Acetoxylacetamido)-4-methyl-5-α-4-azaandrostan-3-one,

4-Methyl-17-(4-(2-nitrophenoxy)-butyroylamido)-5-α-4-azaandrostan-3-one,

17-Isobutyroylamido-4-methyl-5-α-4-zazaandrostan-3-one,

17-(3,3-Dimethyl-4-(1-(4-isobutylphenyl)ethoxy)benzamido)-4-methyl-5-α-4-aza--androstan-3-one,

17-(4-Benzyloxybenzamido)-methyl-5-α-4-azaandrostan-3-one,

4-Methyl-17-(3-fluoro-2-methylbenzamido)-5-α-4-azaandrostan-3-one,

4-Methyl-17-(3,5,5,-trimethylhexanoylamino)-5-α-4-azaandrostan-3-one,

17-((Benzylthio)acetamido)-4-methyl-5-α-4-azaandrostan-3-one,

17-(2-Acetoxyisobutyramido)-4-methyl-5-α-4-azaandrostan-3-one,

4-Methyl-17-trifluoroacetamido-5-α-4-azaandrostan-3-one,

17-(2-Hydroxyisobutyramido)-4-methyl-5-α-4-azaandrostan-3-one,

17-(Isonicotinoylamino)-4-methyl-5-α-4-azaandrostan-3-one,

17-(t-Butylacetamido)-4-methyl-5-α-4-azaandrostan-3-one,

4-Methyl-17-phenylacetamido-5-α-4-azaandrostan-3-one,

4-Methyl-17-(picolinoylamido)-5-α-4-azaandrostan-3-one,

4-Methyl-17-(nicotinoylamido)-5-α-4-azaandrostan-3-one,

17-(3-((3-Benzamido)phenyl)propionamido)-4-methyl-5-α-4-azaandrostan-3-one,

17-Formamido-4-methyl-5-α-4-azaandrostan-3-one,

17-(2-(Carbomethoxy)-1-cyclopentenylcarboxamido)-4-methyl-5-α-4-azaandrostan-3-one,

17-(2,6-Difluorobenzamido)-4-methyl-5-α-4-azaandrostan-3-one, or

17-(2,3-Difluorobenzamido)-4,7-dimethyl-5-α-4-azaandrostan-3-one.

10. The compound according to Claim 8 and the pharmaceutically acceptable salts thereof, wherein the compound is selected from:

17ß(12-(t-Butylthio)dodecanoylamido)-4-methyl-4-aza-5α-androst-1-en-3-one,

4-Methyl-17ß(8-(carbomethoxy)octanoylamido)-4-aza-5α-androst-1-en-3-one,

17ß(Isopropylthiododecanoylamido)-4-methyl-4-aza-5α-androst-1-en-3-one,

17-Benzoylamido-5-α-4-methyl-4-azaandrostan-1-en-3-one,

17-(2-Thiophenesulfonamido)-5-α-4-methyl-4-azaandrostan-1-en-3-one,

4-Methyl-17-(phenylthioacetamido)-5-α-4-methyl-4-azaandrostan-1-en-3-one,

4-Methyl-17-(4-methylpentanoylamido)-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(3-thenoylamino)-5-α-4-azaandrostan-1-en-3-one,

17-(3-(4'-Fluoro-3,5,3'-trimethylbiphen-2-yl)propionamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(6-(Diethylphosphono)hexanoylamino)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-((t-Butylthio)acetamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(3-thiophenacetamido)-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(4-nitrobenzamido)-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(3-nitrobenzamido)-5-α-4-azaandrostan-1-en-3-one,

17-(2-Fluorobenzamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(4-cyanobenzamido)-4-methyl-5-α-4-zazaandrostan-1-en-3-one,

17-(Benzthiophen-3-ylacetamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(2-thiophenecarboxamido)-5-α-4-azaandrostan-1-en-3-one,

17-(1-Methyl-2-pyrrolecarboxamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(4-Carboxy-4methylpentanoylamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(4-Carbomethoxy-4-methylpentanoylamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(4-Carbomethoxy-3,3-dimethylbutyroylamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(3-phenylbutyroylamido)-5-α-4-azaandrostan-1-en-3-one,

17-(2,3-Difluorobenzoylamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(2-methylbenzoylamido)-5-α-4-azaandrostan-1-en-3-one,

17-(2,3-Dimethylbenzamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-Cinnamoylamido-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(3,3-Dimethylacrylamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(3,4-Dimethoxybenzamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(Acetoxylacetamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(4-(2-nitrophenoxy)-butyroylamido)-5-α-4-azaandrostan-1-en-3-one,

17-Isobutyroylamido-4-methyl-5-α-4-zazaandrostan-1-en-3-one,

17-(3,3-Dimethyl-4-(1-(4-isobutylphenyl)ethoxy)benzamido)-4-methyl-5-α-4-aza--androstan-1-en-3-one,

17-(4-Benzyloxybenzamido)-methyl-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(3-fluoro-2-methylbenzamido)-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(3,5,5,-trimethylhexanoylamino)-5-α-4-azaandrostan-1-en-3-one,

17-((Benzylthio)acetamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(2-Acetoxyisobutyramido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-trifluoroacetamido-5-α-4-azaandrostan-1-en-3-one,

17-(2-Hydroxyisobutyramido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(Isonicotinoylamino)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(t-Butylacetamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-phenylacetamido-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(picolinoylamido)-5-α-4-azaandrostan-1-en-3-one,

4-Methyl-17-(nicotinoylamido)-5-α-4-azaandrostan-1-en-3-one,

17-(3-((3-Benzamido)phenyl)propionamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-Formamido-4-methyl-5-α-4-azaandrostan-1-en-3-one,

17-(2-(Carbomethoxy)-1-cyclopentenylcarboxamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

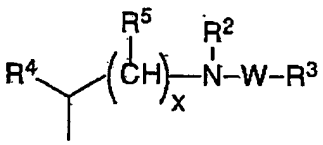
17-(2,6-Difluorobenzamido)-4-methyl-5-α-4-azaandrostan-1-en-3-one,

or

17-(2,3-Difluorobenzamido)-4,7-dimethyl-5-α-4-azaandrostan-1-en-3-one.

11. A compound according to Claim 1 and the pharmaceutically acceptable salts thereof, wherein:

A is:



R^1 is:

H,
methyl or ethyl;

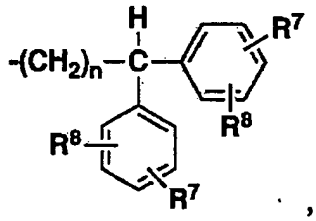
R^2 is:

H, or
C_{1-12} alkyl;

R^3 is:

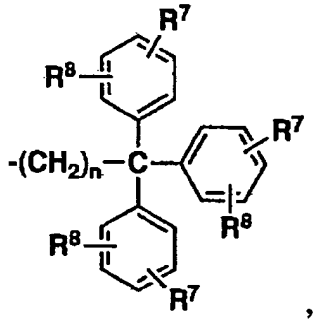
H,
C_{1-20} alkyl,
C_{6-14} aryl,
heteroaryl,
C_{6-14} arylC_{1-20}alkyl,
heteroarylC_{1-20}alkyl,
C_{1-20}alkylthioC_{1-20}alkyl,
C_{1-20}alkylsulfinylC_{1-20}alkyl,
C_{1-20}alkylsulfonylC_{1-20}alkyl,
C_{1-20}alkyloxycarbonylC_{1-20}alkyl,
carboxylC_{1-20}alkyl,

C_{1-20} alkylcarbonylC_{1-20}alkyl,
C_{3-20}cycloalkyl,
C_{3-20}cycloalkylC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
heteroarylC_{1-20}alkyloxycarbonylC_{1-20}alkyl,
haloC_{1-20}alkyl,
hydroxyC_{1-20}alkyl,
halohydroxyC_{1-20}alkyl,
thiosulfatoC_{1-20}alkyl,
C_{6-14} arylC_{1-20}alkyloxyC_{1-20}alkyl,
C_{6-14} arylcarbonylC_{6-14}arylC_{1-20}alkyl,
diarylC_{1-20}alkyl of the formula:



, n equals 0-19;

triarylC_{1-20}alkyl of the formula:



, n equals 1-19; or

C_{2-20} alkenyl,
C_{2-20} alkenylC_{1-20}alkyl,
heteroarylC_{2-20}alkenyl,
C_{6-14} arylC_{2-20}alkenyl,
C_{2-20}alkynylC_{1-20}alkyl,

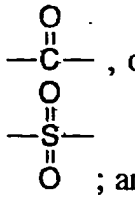
C_{6-14} arylC_{2-20}alkynylC_{1-20}alkyl, or
heteroarylC_{2-20}alkynylC_{1-20}alkyl;

R^4 is:

H,
C_{1-20} alkyl,
C_{6-14} aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen; or
heteroaryl;

R^5 can be the same or different when x is greater than 1 and is:
H, or
C_{1-20} alkyl;

W is:



; and

x is an integer from 1-10.

12. A compound according to Claim 11 and the pharmaceutically acceptable salts thereof, wherein

R^1 is:

H,
methyl, or
ethyl;

R^2 is:

H,
methyl,
ethyl, linear or branched:
propyl,
butyl,
pentyl,
hexyl, or heptyl;

R^3 is:

t-butyl,
3-thienyl,
2-thienyl,
11-(isopropylthio)undecyl,
7-(carbomethoxy)heptyl,
1-(1-(4-isobutylphenyl-)ethyl,
7-(carboxy)heptyl,
acetylmethyl,
1-adamantylmethyl,
2-thienylmethyl,
2-(carbobenzyloxy)ethyl,
3,4-dimethoxyphenylmethyl,
phenyl,
5-bromopentyl,
11-hydroxyundecyl,
1-(4-nitrophenyl)ethyl,

isopropylthiomethyl,
5-(thiosulfato)pentyl,
benzyloxymethyl,
carbomethoxymethyl,
diphenylmethyl,
triphenylmethyl,
2-furyl,
4-isopropylphenyl,
cyclohexylmethyl,
4-methylcyclohexyl,
3-(3-indolyl)propyl,
3-Indolylmethyl,
4-isobutylbenzyl,
4-nitrobenzyl,
3-acetamidomethyl,
4-ethoxybenzyl,
hexadecyl,
(isopropylthio)methyl,
stearyl,
3,5-Bis(trifluoromethyl)benzyl,
3-cyanobenzyl,
heptafluoropropyl,
4-benzoylbenzyl,
5-benztriazolyl,
3,5-difourobenzyl,
bis(4-isopropylphenyl)methyl,
2-hydroxybenzyl,
phenylvinyl,
2-hydroxy-3,3,3-trichloropropyl,
methyl,
allyl,
n-propyl,
n-octyl,
isopropyl,

isobutyl,
ethyl,
benzyl,
octadecyl,
2(ethyl)phenyl,
3(chloro)phenyl,
4(methyl)phenyl,
2,3(dichloro)phenyl,
4(fluoro)phenyl,
3(methoxy)phenyl,
2(ethoxy)phenyl,
2-napthyl, or
2-thiazolyl;

R^4 is:

H,
methyl,
ethyl, linear or branched:
propyl,
butyl,
C_6 aryl wherein aryl is a monocyclic system composed of 6-membered aromatic rings either unsubstituted or substituted with R wherein R is H, C_{1-6} alkyl, arylC_{1-20}alkyl with the alkyl groups unsubstituted or substituted with hydroxyl, C_{1-8}alkyloxy, carboxy C_{0-10}alkyl, or halogen or aryl directly substituted independently with amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino, mono C_1-C_4 alkylaminoaryl, di C_1-C_4 alkylaminoaryl, hydroxyl, haloC_{1-20}alkyl, carboxamido, benzoyl, C_{1-20}alkyloxy, C_{1-20}alkyl, C_{2-20}alkenyl, cyano, nitro, acetamide or halogen; or

heteroaryl;

R^5 can be the same or different when x is greater than 1 and is:
H,
methyl,
ethyl,
propyl,
butyl, or
pentyl.

13. The compound according to Claim 12, selected from:

4-Methyl-20-(4-Nitrobenzamidomethyl)-4-aza-5α-pregnan-3-one,

20-(3,4-Dimethoxyphenylacetamidomethyl)-4-methyl-4-aza-5α-pregnan-3-one,

4-Methyl-20-(Palmitoylamidomethyl)-4-aza-5α-pregnan-3-one,

20-(Heptafluorobutyramidomethyl)-4-methyl-4-aza-5α-pregnan-3-one, or

4-Methyl-20(salicylamidomethyl)-4-aza-5α-pregnan-3-one.

14. The compound according to Claim 12, selected from:

4-Methyl-20-(4-nitrobenzamidomethyl)-4-aza-5α-1-pregnen-3-one,

20-(3,4-Dimethoxyphenylacetamidomethyl)-4-methyl-4-aza-5α-1-pregnen-3-one,

4-Methyl-20-(palmitoylaminomethyl)-4-aza-5α-1-pregnen-3-one,

20(Heptafluorobutyramidomethyl)-4-methyl-4-aza-5α-1-pregnen-3-one, or

4-Methyl-20(Salicylamidomethyl)-4-aza-5α-1-pregnen-3-one.

15. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in a pharmaceutically acceptable carrier therefor.

16. A method of treating benign prostatic hyperplasia, acne, female hirsutism, male pattern baldness, androgenic alopecia, prostatitis, and/or preventing prostatic carcinoma in a human host in need of such treatment comprising the step of administering to said host a therapeutically effective amount of the compound defined in Claim 1.

17. The method of Claim 16 wherein said compound is an inhibitor of 5α-reductase 1.

18. The method of Claim 16 wherein said compound is an inhibitor of 5α-reductase 2.

19. The method of Claim 16 wherein said compound is a dual inhibitor of both 5α-reductase 1 and 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04633

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61K31/435 C07D 221/02
US CL :546/77; 514/284
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 546/77; 514/284

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS online structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Jour. Clinical Endoc. and METAB, Vol. 74 1992, Diani et al. "HAIR GROWTH EFFECTS OF ORAL ADMINISTRATION OF FINASTERIDE, a steroid 5α reductase inhibitor, alone and in combination with topical minoxidil in the balding stumptail macaque, pages 345-350. See page 345, para. bridging cols. 1-2, last 3 lines.	16-19
A	J. Org. Chem., Vol. 46, 1981, Back "Oxidation of Azasteroid Lactams and Alcohols with Benzeneselenic Anhydride" pages 1442-6	1-19

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
13 JULY 1993

Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04633

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Jour. Med. Chem., Vol. 27, 1984, Rasmusson et al. "Azasteroids as inhibitors of rat prostatic 5α reductase" pages 1690-1701	1
X	Jour. Med. Chem., Vol. 29, 1986 Rasmusson et al. "Azasteroids structure-activity relationships for inhibition of 5α reductase and of androgen receptor binding" pages 2298-2315. See page 2300 compounds 10A2, 10BA and rest of list.	1
A	E, P, B 0200 859 (Cainelli et al.) 12 November 1986. See entire document.	1
X	US, A, 4,377,584 (Rasmusson et al.) 22 March 1983. See claims 1, 14, 16-18	1, 2, 7-10, 15-19
A	US, A, 4,760,071 (Rasmusson et al.) 26 July 1988. See entire document.	1
A	US, A, 4,882,319 (Holt et al.) 21 November 1989. See entire document.	1
A	US, A, 5,049,562 (Rasmusson et al.) 17 September 1991. See entire document.	1
X, P	US, A, 5,116,983 (Bhattacharya et al.) 26 May 1992. See entire document.	1, 2, 7-10, 15-19
A	US, A, 5,110,939 (Holt et al.) 5 May 1992. See entire document.	1
A	Jour. Organic Chem. Vol. 54; 1989 Back et al. "N Chloro Azasteroids A Novel Class of Reactive Steroid Analogues. Preparation, Reaction with Thiols and Photochemical Conversion to Electrophilic Nacyol Imines" pages 1904-10	1
A	US, A, 4,859,681 (Rasmusson et al.) 22 August 1989.	1-19